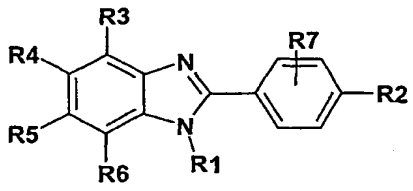
Benzimidazole derivatives

The present invention relates to bicyclic compounds, in particular to benzimidazole derivatives and to pharmaceutical uses thereof.

Accordingly the invention provides compounds of formula (I) or a pharmaceutically acceptable salt or prodrug ester thereof:



(I)

wherein

R1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy, lower alkoxy-lower alkyl, cycloalkyloxy-lower alkyl, lower thioalkyl, lower alkylthio-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, lower alkenyl and lower alkynyl);

R2 is selected from the group consisting of optionally substituted (lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl);

R3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, aryl-lower alkyl, heteroaryl, lower alkenyl, lower alkynyl, heteroaryl, aryl-lower alkyl and heteroaryl-lower alkyl and amino);

R4 is selected from the group consisting of H, halo, cyano, hydroxy, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino) and the group having the formula R8-Z-$(CH_2)_n$-;

wherein Z represents a direct bond or is selected from the group consisting of O, NH, CH_2, CO, SO, SO_2 or S;

wherein R8 is selected from the group consisting of optionally substituted (aryl, heteroaryl, carbocyclic aryl, cycloalkyl, heterocycloalkyl);

and wherein n is 0, 1, 2 or 3;

R5 is selected from the group consisting of H, halo, cyano, hydroxyl, optionally substituted (lower alkyl, lower alkoxy, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl, alkenyl, alkynyl and amino);

R6 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heteroaryl-lower alkyl and amino).

R7 represents one or more substituents independently selected from the group consisting of H, halo, hydroxyl, optionally substituted (lower alkyl, lower alkoxy, amino, cyano, and carbonyl).

The optional substituent or substituents on R1-R8 are independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, sulfinyl, sulfonyl, sulfanyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, sulfinyl, sulfonyl, sulfanyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

For the avoidance of doubt, the terms listed below are to be understood to have the following meaning throughout the present description and claims:

The term "lower", when referring to organic radicals or compounds means a compound or radical with may be branched or unbranched with up to and including 7 carbon atoms.

A lower alkyl group may be branched, unbranched or cyclic and contains 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Lower alkyl represents, for example: methyl, ethyl, propyl, butyl, isopropyl, isobutyl, tertiary butyl or 2,2-dimethylpropyl.

A lower alkoxy group may be branched or unbranched and contains 1 to 7 carbon atoms, preferably 1 to 6 carbon atoms. Lower alkoxy represents, for example: methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy. Lower alkoxy includes cycloalkyloxy and cycloalkyl - lower alkyloxy.

A lower alkene, alkenyl or alkenoxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1 to 4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene, lower alkenyl or lower alkenyloxy represents for example vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl and the oxy equivalents thereof.

A lower akyne or alkynyl group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1 to 4 carbon atoms and contains at least one carbon-carbon triple bond. Lower alkyne or lower alkynyl or lower alkenyloxy represents for example ethynyl or propynyl.

In the present application, oxygen containing substituents, e.g. alkoxy, alkenyloxy, alkynyloxy, carbonyl, etc. encompass their sulphur containing homologues, e.g. thioalkyl, alkyl-thioalkyl, thioalkenyl, alkenyl-thioalkyl, thioalkynyl, thiocarbonyl, sulphone, sulphoxide etc.

Halo or halogen represents chloro, fluoro, bromo or iodo.

Aryl represents carbocyclic aryl, heterocyclic aryl or biaryl.

Carbocyclic aryl is an aromatic cyclic hydrocarbon containing from 6 to 18 ring atoms. It can be monocyclic, bicyclic or tricyclic, for example naphthyl, phenyl, or phenyl mono-, di- or trisubstituted by one, two or three substituents.

Heterocyclic aryl is an aromatic monocyclic or bicyclic hydrocarbon containing from 5 to 18 ring atoms one or more of which are heteroatoms selected from O, N or S. Preferably there

are one or two heteroatoms. Heterocyclic aryl represents, for example: pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, oxadiazolyl, benzimidazolyl. Heterocyclic aryl also includes such substituted radicals.

Cycloalkyl represents a cyclic hydrocarbon containing from 3 to 12 ring atoms preferably from 3 to 6 ring atoms. Cycloalkyl represents, for example: cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The cycloalkyl may optionally be substituted.

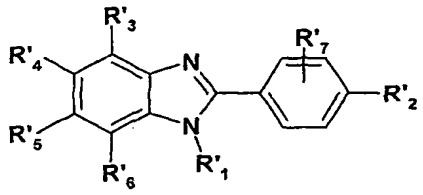
Heterocycloalkyl represents a mono-, di- or tricyclic hydrocarbon which may be saturated or unsaturated and which contains one or more, preferably one to three heteroatoms selected from O, N or S. Preferably it contains between three and 18 ring atoms. The term heterocycloalkyl is intended also to include bridged heterocycloalkyl groups such as 3-hyroxy-8-aza-bicyclo[3.2.1]oct-8-yl.

Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example mineral acids, e.g. hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example aliphatic or aromatic carboxylic or sulfonic acids, e.g. acetic, trifluoroacetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxylmaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

The agents of the invention which comprise free hydroxyl groups may also exist in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding agents of the invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable prodrug esters are those derived

from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

A second aspect of the invention provides a compound of formula (I') or a pharmaceutically acceptable salt, or prodrug ester thereof:



(I')

wherein

R'_1 is selected from the group consisting of optionally substituted (C_1-C_6 alkyl, lower alkoxy-lower alkyl, lower alkynyl, lower thioalkyl-lower alkyl, cycloalkyl-lower alkyl);

R'_2 is lower alkyl;

R'_3 is selected from the group consisting of halo, cyano, optionally substituted (lower alkyl, lower alkoxy, lower thioalkyl, lower thioalkenyl, lower alkynyl, aryl and aryl-lower alkyl);

R'_4 is selected from the group consisting of H, halo, cyano, optionally substituted (lower alkyl, aryl, aryl-lower alkyl, heteroaryl, heteroaryl-lower alkyl) and the group having the formula R'_8-$Z(CH_2)_n$-;

wherein Z represents a direct bond or is selected from the group consisting of O, NH, CH_2, CO, SO, SO_2 or S;

wherein R'_8 is selected from the group consisting of optionally substituted (aryl, pyrazolyl, thiazolyl, cyclobutyl, tetrazolyl, pyridyl, indazolyl, pyrazinyl, furanyl, isoxazolyl, pyrrolidinyl, benzimidazolyl, imidazolyl, oxazolyl);

and wherein n is 0, 1, 2 or 3;

R'_5 is H, halo, or lower alkyl;

R'_6 is selected from the group consisting of halo, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkynyl);

R'_7 represents one or more substituents independently selected from the group consisting of H, halo, hydroxyl, optionally substituted (lower alkyl, lower alkoxy, amino, cyano, and carbonyl);

the optional substituent or substituents on R'_1-R'_8 being independently selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, sulfinyl, sulfonyl, sulfanyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl; all of which, except halogen, are independently optionally substituted by one or more substituents, selected from the group consisting of halogen, hydroxy, lower alkyl, mono or di-lower alkylamino, aminocarbonyl, sulfinyl, sulfonyl, sulfanyl, mono or di-lower alkylaminocarbonyl, amino, carboxy, lower alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{18} heterocycloalkyl, lower alkylcarbonyl, lower alkoxycarbonyl, nitryl, aryl.

With reference to formula I and I', preferably R3 or R'_3 is halo, ethyl or substituted methyl. For example, R3 or R'_3 may be Br, I or CF_3. More preferably, R3 or R'_3 is Br. Alternatively preferably, R3 or R'_3 is trifluoromethyl. Alternatively preferably, R3 or R'_3 is ethynyl.

R7 or R'_7 is preferably located at the 2 and/or 2' position of the phenyl ring.

Preferred compounds of formula I are:

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

4-Bromo-1-propyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

4-Bromo-1-butyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

4-Bromo-1-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethyl}-dimethyl-amine

4-Chloro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-phenyl-1H-benzoimidazole

3-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol

2-(4-Isopropyl-phenyl)-7-methoxy-4-[3-(2-methoxy-ethoxy)-phenyl]-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-(3,5-Dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Methyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Ethylsulfanyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

4-Bromo-1-cyclopropylmethyl-2-(4-cyclopropyl-phenyl)-7-methoxy-1H-benzoimidazole

5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4,5-Dibromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4,5-Dibromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4,5-Dibromo-2-(4-isopropyl-2-methoxy-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Iodo-5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Bromo-4-iodo-2-(4-isopropyl-2-methoxy-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzoimidazole

4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-5-trifluoromethyl-1H-benzoimidazole

4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Bromo-4-ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

4-Bromo-5-fluoro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Benzyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Benzyl-4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Benzyl-4-ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-cyclobutylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(3-fluoro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(3-chloro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-thiazol-2-ylmethyl-1H-benzoimidazole

4-Bromo-5-(3,5-difluoro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-ylmethyl-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfonyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-2-ylmethyl-1H-benzoimidazole

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(3,4-dimethoxy-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-pyridin-2-ylmethyl)-1H-benzoimidazole

5-Benzyl-4-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(3-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(3-methoxy-phenyl)-methanone

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanone

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(1-phenyl-ethyl)-1H-benzoimidazole

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile

4-Isobutyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenyl-1H-benzoimidazole

4-Bromo-5-(3,4-dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenol

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester

4-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-yl-1H-benzoimidazole

3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzonitrile

1-{5-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-2-methoxy-phenyl}-ethanone

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzonitrile

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-4-yl-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(4-methyl-pyrazol-1-ylmethyl)-1H-benzoimidazol

4-Bromo-5-imidazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(4-bromo-5-methyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(4-bromo-3-methyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-5-(3,5-dimethyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

1-[4-Bromo-1-(2-hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid ethyl ester

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methoxymethyl-imidazol-1-ylmethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-imidazol-1-ylmethyl)-1H-benzoimidazole

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-benzoimidazol-2-ol

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzoimidazol-1-ylmethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzoimidazol-1-ylmethyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzoimidazol-1-ylmethyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

3-[4-Bromo-1-(2-hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazol-5-ylmethyl]-3H-imidazole-4-carboxylic acid methyl ester

2-[4-Bromo-5-imidazo[4,5-b]pyridin-3-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethanol

2-[4-Bromo-5-indazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethanol

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(5-methyl-tetrazol-2-ylmethyl)-benzoimidazol-1-yl]-ethanol

4-Bromo-5-(4-bromo-5-methyl-pyrazol-1-ylmethyl)-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(4-methyl-pyrazol-1-ylmethyl)-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

4-Bromo-5-isopropoxymethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-pyrrolidin-2-one

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenylsulfanyl-1H-benzoimidazole

5-Benzenesulfinyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

5-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-2-ylmethyl-4-trifluoromethyl-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyrazol-1-ylmethyl-4-trifluoromethyl-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenoxy methyl-1H-benzoimidazole

2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-ethanol

2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol

{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-methanol

N-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-acetamide

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-benzamide

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-benzenesulfonamide

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenylamine

1-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-ethanone

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenol

2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-pyridin-3-ol

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxymethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methoxy-phenoxymethyl)-1H-benzoimidazole

{3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-2-methyl-phenyl}-methanol

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-3-yloxymethyl)-1H-benzoimidazole

4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfonyl-phenoxymethyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

2-{3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol

2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-acetamide

2-{2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol

2-{2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-phenyl}-ethanol

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-phenyl-amine

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-(2-methanesulfonyl-phenyl)-amine

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-[2-(2-methanesulfonyl-ethyl)-phenyl]-amine

2-(2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-amino}-phenyl)-acetamide

2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-be nzoimidazol-5-ylmethyl]-amino}-benzenesulfonic acid

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-(2-fluoro-phenyl)-amine

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-pyridin-2-yl-amine

2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-amino}-benzoic acid methyl ester

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-pyridin-3-yl-amine

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-methyl-phenyl-amine

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-(3-methanesulfonyl-phenyl)-amine

2-(2-{[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-amino}-phenyl)-acetamide

[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-(2-methanesulfonyl-phenyl)-amine

[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-[2-(2-methanesulfonyl-ethyl)-phenyl]-amine

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid methyl ester

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid dimethylamide

1-{1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazol-2-yl}-ethanone

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-indole-2,3-dione

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-oxazol-2-ylmethyl-1H-benzoimidazole

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carbonitrile

1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid methylamide

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-bromo-4-trifluoromethyl-1H-benzoimidazole

[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-phenyl-amine

[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-pyridin-2-yl-amine

2-{[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-amino}-benzenesulfonamide

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenoxymethyl-4-trifluoromethyl-1H-benzoimidazole

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxymethyl)-4-trifluoromethyl-1H-benzoimidazole

2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-benzenesulfonamide

4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxy)-1H-benzoimidazole

According to a third aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) in association with a pharmaceutically acceptable excipient, diluent or carrier.

According to a fourth aspect of the invention there is provided a compound of formula (I) for promoting the release of parathyroid hormone.

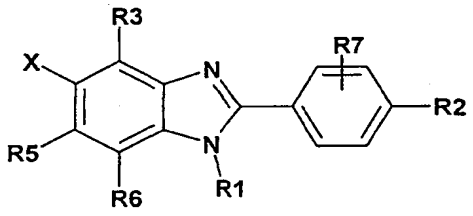
It is now well established that controlled treatment of patients with parathyroid hormone (PTH) and analogues and fragments thereof can have a pronounced anabolic effect on bone formation. Thus compounds which promote PTH release, such as the compounds of the present invention may be used for preventing or treating conditions of bone which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Thus in a fifth aspect the invention includes a method for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable in which an

effective amount of a compound of formula (I) as defined above, or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof is administered to a patient in need of such treatment.

In a sixth aspect the invention provides a process for preparation of a compound of formula (I) in free or salt form, comprising:

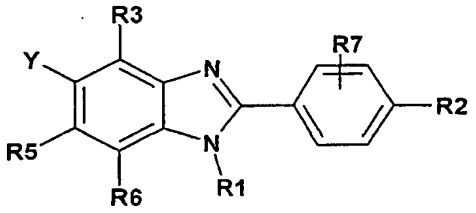
(a) introducing a group R4 into a corresponding compound of formula II, R4 being as defined above:



(II)

wherein X is any suitable group capable of substitution by R4 and wherein R1; R2, R3, R5, R6 and R7 are as defined above; or

(b) for the preparation of compounds wherein R4 is an aryl-CH_2 group, appropriately introducing such aryl group by reaction with a compound of formula III:



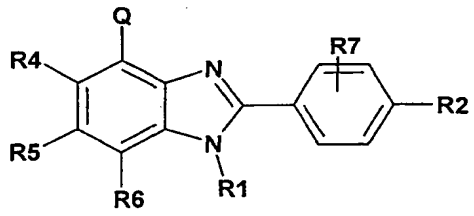
(III)

wherein Y denotes either:

(i) a leaving group-CH_2- and R1, R2, R3, R5, R6 and R7 are as defined above; or

(ii) the group –CH=O; or

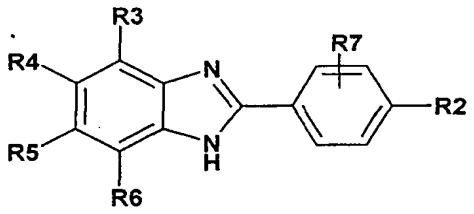
(c) introducing a group R3 into a corresponding compound of formula IV, R3 being as defined above:



(IV)

wherein Q is any suitable group capable of substitution by R3 and wherein R1, R2, R4, R5, R6 and R7 are as defined above; or

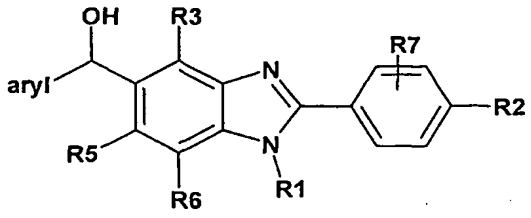
(d) appropriately N-substituting a corresponding compound of formula V by a group R1 as defined above:



(V)

wherein R2-R7 are as defined above; or

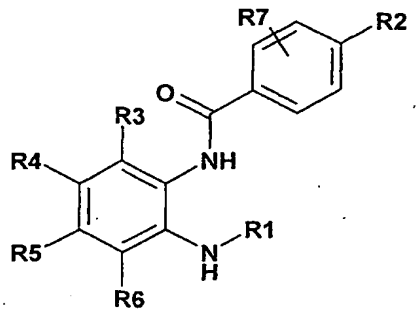
(e) for the preparation of compounds wherein R4 is aryl-CO-, oxidizing a compound of formula (VI):



(VI)

with a suitable oxidizing agent, R1, R2, R3, R5, R6 and R7 being as defined above;

(f) treating a compound of formula (VII):



(VII)

under suitable conditions to effect ring closure, R1-R7 being as defined above;
[***Marc, can we use this reaction for all cpds of formula (I), or only when certain substituents are present?****]**

transforming the resultant compound into further compound of formula I if appropriate;

and recovering the resultant compounds of formula I in free or salt form.

The process of the invention is effected in a conventional manner. In process variant (a), X is conveniently an iodide group and the transformation is suitably performed by Suzuki coupling, for example by reacting compound II with aryl or heteroaryl-$B(OH)_2$ in the presence of a palladium catalyst. In process variant (b), Y is conveniently a methanesulfonic acid methyl ester group and compound III may be reacted with the desired aryl or heteroaryl R4 group in the presence of a base such as sodium hydride in a suitable solvent such as DMF. Alternatively in process variant (b), when Y denotes the group –CH=O, the compound of formula (III) may be reacted with a Grignard reagent denoted by arylMgBr in a suitable solvent e.g. THF to produce, after subsequent treatment with phosphinic acid and iodine, the corresponding compound of formula (I). In process variant (c), R3 may for example represent a bromo group which may be introduced by reacting N-bromosuccinimide or Br_2 / acetic acid in a suitable solvent with a compound of formula IV wherein Q denotes H. Process variant (d) is an N-alkylation in which R1 is conveniently an alkyl group and may be introduced by reacting a corresponding bromoalkyl with a compound of formula V in the presence of a base such as sodium hydride in suitable solvent, for example DMF. A suitable oxidizing agent in process (e) is for example oxalyl chloride in DMSO in a Swern oxidation

reaction. In process variant (f), ring closure is conveniently effected by heating to 100°C with acetic acid.

If desired, the compound obtained may be further transformed into another compound of formula I. For example, an aryl ring substituent OH may be transformed to a 2-methoxy-ethoxy group conveniently by reaction with 2-(bromoethyl)-methyl ether in the presence of a base.

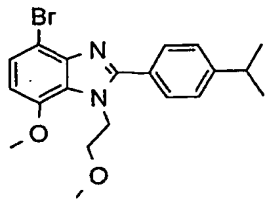
The compounds of formula I in free form may be converted into salt forms in conventional manner and vice-versa.

The compounds of the invention can be recovered from the reaction mixture and purified in conventional manner. Isomers, such as enantiomers, may be obtained in conventional manner, e.g. by fractional crystallization or asymmetric synthesis from corresponding asymmetrically substituted, e.g. optically active starting materials.

In a seventh aspect invention includes the use of a compound of formula (I) in the manufacture of a medicament for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Agents of the invention may be prepared by processes described below:

Example 1: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



To a stirred solution of 500mg (1.45mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole in 11ml DMF, NaH (38mg, 1.6mmol) is added and stirring is continued for 1h

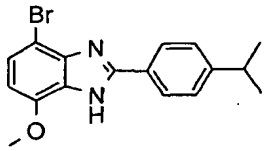
at RT, and then the reaction mixture is heated to 60°C. 0.152ml (0.175mmol) (2-bromoethyl)-methyl ether is added and stirring is continued at this temperature for another 6h. The reaction mixture is cooled to room temperature, poured into water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 398mg of the title compound as colorless oil.

R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 403 $(M+1)^+$ (^{79}Br), 405 $(M+1)^+$ (^{81}Br)

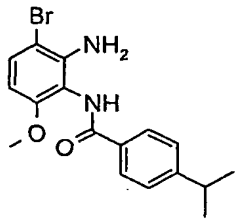
The starting materials can be prepared as follows:

a) 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole:



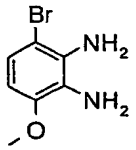
A solution of 1.44g (3.97mmol) N-(2-amino-3-bromo-6-methoxy-phenyl)-4-isopropyl-benzamide in 25ml glacial acetic acid is stirred at 100°C for 3h. The reaction mixture is cooled to room temperature 200ml ethyl acetate is added. The solution is washed with 4N NaOH (2x) and with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 1.12g of the title compound as slightly reddish solid.

b) N-(2-Amino-3-bromo-6-methoxy-phenyl)-4-isopropyl-benzamide:



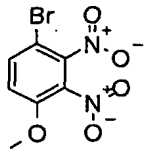
A solution of 870mg (4.01mmol) 3-bromo-6-methoxy-benzene-1,2-diamine, 1.16g (6.0mmol) EDC, 744mg (6.0mmol) DMAP and 707mg (4.01mmol) 4-isopropylbenzoic acid in 20ml dichloromethane is stirred at room temperature for 72h. The reaction mixture is concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 1.44g of the title compound as a slightly reddish solid.

c) 3-bromo-6-methoxy-benzene-1,2-diamine:



A solution of 1.12g (4.04mmol) 1-bromo-4-methoxy-2,3-dinitro-benzene in 25ml THF is hydrogenated in the presence of 100mg Raney-Nickel (B113W Degussa) at normal pressure for 3h. The catalyst is filtered off and the filtrate is concentrated in vacuo to afford 871mg of the title compound as a grey crystalline solid.

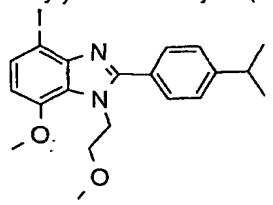
d) 1-Bromo-4-methoxy-2,3-dinitro-benzene:



1.0g (4.3mmol) 4-bromo-3-nitroanisole is nitrated by dropwise addition of 1.0ml of a mixture of 0.4 ml nitric acid (100%) and 0.6ml concentrated sulfuric acid. Stirring is continued for 1h. After that the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water and brine (2x), dried over $MgSO_4$, filtered

and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 630mg of the title compound as yellow crystals.

Example 2: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



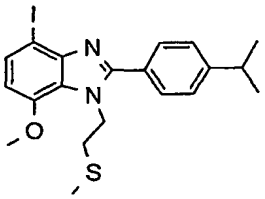
The title compound is prepared starting from 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound is obtained as a colorless oil.

R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 451 $(M+1)^+$

The starting material 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole is prepared from 4-iodo-3-nitro-anisole using exactly the same methodology as described for in Example 1 a)-d).

Example 3: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

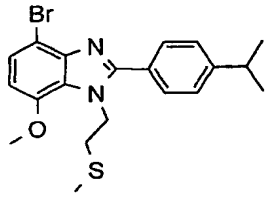


Using 1-bromo-2-methylsulfanyl-ethane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.47min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 467 $(M+1)^+$

Example 4: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

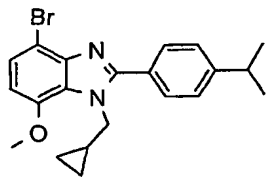


Using 1-bromo-2-methylsulfanyl-ethane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.36min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 419 $(M+1)^+$ (^{79}Br), 421 $(M+1)^+$ (^{81}Br)

Example 5: 4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

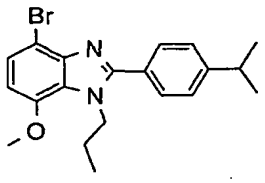


Using bromomethyl-cyclopropane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.34min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 399 $(M+1)^+$ (^{79}Br), 401 $(M+1)^+$ (^{81}Br)

Example 6: 4-Bromo-1-propyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

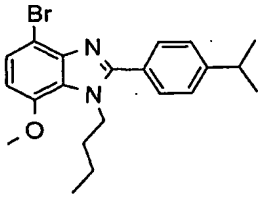


Using 1-bromo-propane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 387 $(M+1)^+$ (^{79}Br), 389 $(M+1)^+$ (^{81}Br)

Example 7: 4-Bromo-1-butyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

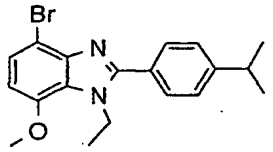


Using 1-bromo-butane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.41min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 401 $(M+1)^+$ (^{79}Br), 403 $(M+1)^+$ (^{81}Br)

Example 8: 4-Bromo-1-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole

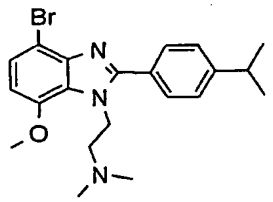


Using 1-bromo-ethane instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 373 $(M+1)^+$ (^{79}Br), 375 $(M+1)^+$ (^{81}Br)

Example 9: {2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethyl}-dimethyl-amine

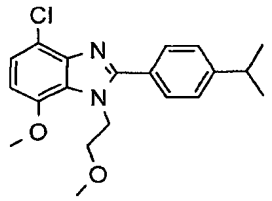


Using (2-Bromo-ethyl)-dimethyl-amine instead of (2-bromoethyl)-methyl ether the title compound is prepared using the same reaction conditions as described for the preparation of Example 1.

R_t = 1.86min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 416 $(M+1)^+$ (^{79}Br), 418 $(M+1)^+$ (^{81}Br)

Example 10: 4-Chloro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



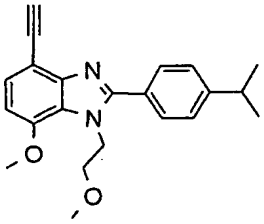
The title compound is prepared starting from 4-chloro-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound is obtained as a colorless oil.

R_t = 2.18min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 359 $(M+1)^+$

The starting material 4-chloro-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole is prepared from 4-chloro-3-nitro-anisole using exactly the same methodology as described in Example 1 a)-d).

Example 11: 4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

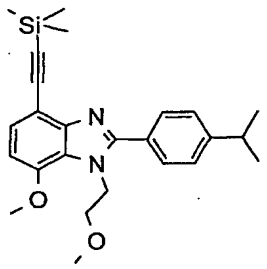


A mixture of 17mg (0.04mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trimethylsilanylethynyl-1H-benzoimidazole and 0.5ml 1N NaOH in 2ml THF/methanol (1:1) is stirred for 1hour at 60°C. The reaction mixture is cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified on 0.5mm silica gel plates (hexane:EtOAc = 3:1) to afford 7mg of the title compound as yellow oil.

R_t = 2.11min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

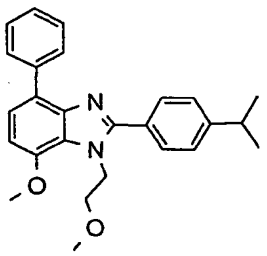
MS: 349 $(M+1)^+$

2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trimethylsilanylethynyl-1H-benzoimidazole can be prepared using the following procedure:



A mixture of 50mg (0.111mmol) 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 0.1ml (0.77mmol) triethylamine, 0.1ml (0.7mmol) ethinyltrimethylsilane and 5mg palladium-II-acetate in 1ml acetonitrile is stirred at 50°C for 3hours. Then the reaction mixture is cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 17mg of the title compound as colorless oil.

Example 12: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-phenyl-1H-benzoimidazole

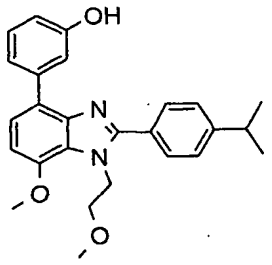


A mixture of 100mg (0.25mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 45mg (0.424mmol) sodium carbonate, 34mg (0.275mmol) phenyl-boronic acid and 10mg tetrakis(triphenylphosphine) palladium in 10ml toluene/water (3:1) is stirred at 100°C for 9 hours. Then the reaction mixture is cooled to room temperature and poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) to afford 53mg of the title compound as a white crystalline solid.

R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 401 $(M+1)^+$

Example 13: 3-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol

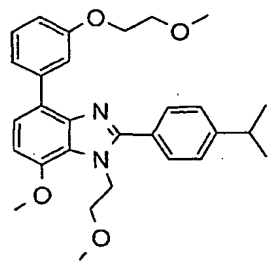


The title compound is obtained using 3-hydroxyphenyl-boronic acid instead of phenyl-boronic acid using the same procedure as described for the preparation of Example 12 as a white crystalline solid.

R_t = 2.07min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 417 $(M+1)^+$

Example 14: 2-(4-Isopropyl-phenyl)-7-methoxy-4-[3-(2-methoxy-ethoxy)-phenyl]-1-(2-methoxy-ethyl)-1H-benzoimidazole

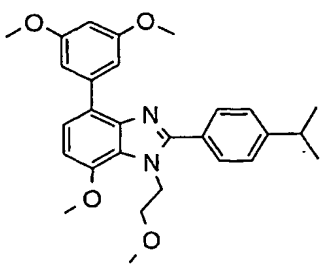


5mg (0.2mmol) NaH is added to a solution of 70mg (0.173mmol) 3-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-4-yl]-phenol in 2ml DMF. This mixture is stirred at room temperature for 1h. After that 28mg (0.207mmol) 2-(bromoethyl)-methyl ether is added and stirring is continued for another 3h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 70mg of the title compound as a colorless oil.

R_t = 2.18min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 475 $(M+1)^+$

Example 15: 4-(3,5-Dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

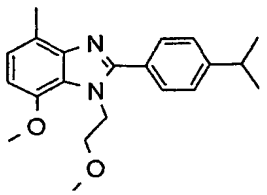


The title compound is obtained using 3,5-dimethoxyphenyl-boronic acid instead of phenyl-boronic acid using the same procedure as described for the preparation of Example 12 as a colorless oil.

R_t = 2.20min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 461 $(M+1)^+$

Example 16: 4-Methyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



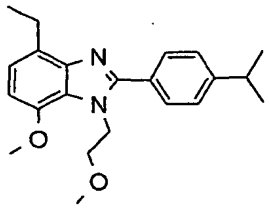
The title compound is prepared starting from 4-methyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole and (2-bromoethyl)-methyl ether using the same reaction conditions as described in Example1. The title compound is obtained as a colorless oil.

R_t = 2.01min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 339 $(M+1)^+$

The starting material 4-methyl-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole is prepared from 4-methyl-3-nitro-anisole using the same method as described in Example 1 a)-d).

Example 17: 4-Ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

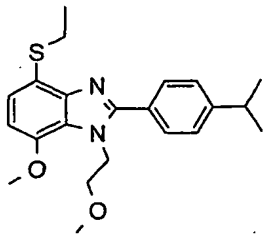


To a solution of 150mg (0.223mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 8ml THF, 0.289ml tert-butyllithium (1.7M in pentane) is slowly added at -78°C. This mixture is stirred for 1h at -78°C then 54µl (0.669mmol) ethyl iodide is added. The reaction mixture is warmed to room temperature and stirring is continued for 12h. The reaction mixture is cooled to room temperature, poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 25mg of the title compound as a colorless oil.

R_t = 2.05min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 353 $(M+1)^+$

Example 18: 4-Ethylsulfanyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



NaH (2.4mg, 0.1mmol) is added to a solution of 7-ethylsulfanyl-2-(4-isopropyl-phenyl)-3-(2-methoxy-ethyl)-3H-benzoimidazol-4-ol (35mg, 0.094mmol) in 1ml DMF. The mixture is stirred at room temperature for 1h and methyl iodide (6µl, 0.1mmol) is added. Stirring is continued for 1h, then the reaction mixture is poured on water and extracted (3x) with ethyl acetate.

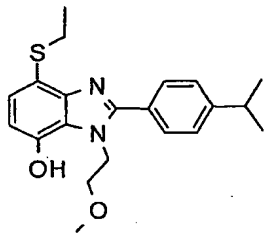
The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) to afford 11mg of the title compound as a colorless oil.

R_t = 2.13 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 385 $(M+1)^+$

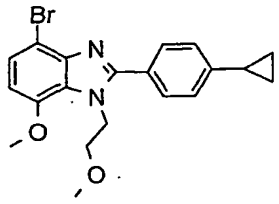
The starting material is prepared as follows:

7-Ethylsulfanyl-2-(4-isopropyl-phenyl)-3-(2-methoxy-ethyl)-3H-benzoimidazol-4-ol



A mixture of 300mg (0.744mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 1) and 313mg (3.72mmol) EtSNa in 2ml DMF is stirred at reflux temperature for 4h. after that the reaction mixture is poured on 10ml conc. HCl, stirred for 10min , diluted with water 25ml and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 35mg of the title compound as a colorless oil.

Example 19: 4-Bromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



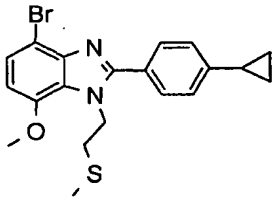
The title compound and the precursors can be prepared using the same synthesis sequence as described in example 1. Instead of 4-isopropylbenzoic acid, 4-cyclopropyl-benzoic acid is used in step b).

R_t = 2.06min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 401 $(M+1)^+$ (^{79}Br), 403 $(M+1)^+$ (^{81}Br)

Similarly, by using the appropriate alkyl-bromides, the following compounds can be prepared:

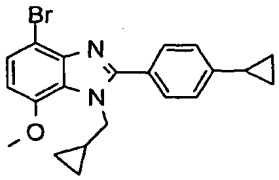
Example 20: 4-Bromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole



R_t = 2.169min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 417 $(M+1)^+$ (^{79}Br), 419 $(M+1)^+$ (^{81}Br)

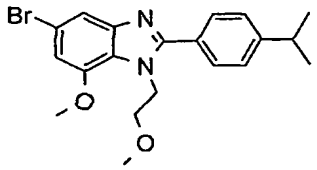
Example 21: 4-Bromo-1-cyclopropylmethyl-2-(4-cyclopropyl-phenyl)-7-methoxy-1H-benzoimidazole



R_t = 2.174min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 397 $(M+1)^+$ (^{79}Br), 399 $(M+1)^+$ (^{81}Br)

Example 22: 5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

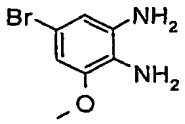


The title compound and the precursors can be prepared using the same synthesis sequence as described in example 1 from 5-Bromo-3-methoxy-benzene-1,2-diamine.

R_t = 2.13min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 403 $(M+1)^+$ (^{79}Br), 405 $(M+1)^+$ (^{81}Br)

a) 5-Bromo-3-methoxy-benzene-1,2-diamine:

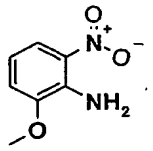


A solution of 2.0g (8.1mmol) 4-Bromo-2-methoxy-6-nitro-phenylamine [Zhou, Q-T., et al. *Huaxue Xuebao* **1980**, *38*(5), 507-10] in 50ml methanol/water (2:1) is hydrogenated in the

presence of 200mg Pt/C (Engelhard 4709) at normal pressure for 3h. Then the catalyst is filtered off and the filtrate is concentrated in vacuo to afford 1.5g of the title compound as an oil.

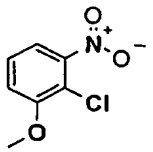
An alternative way for the preparation of the compound described in example 22 is outlined below:

a) 2-Methoxy-6-nitro-phenylamine:



To a stirred solution of 20g (129.9mmol) 2-hydroxy-6-nitroaniline in 150ml DMF, NaH (3.42g, 143mmol, 95%) is added at 0°C and stirring is continued for 1.5h. MeI (9.3ml, 150mmol) is added and the reaction mixture is stirred at room temperature for 1h. After that the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. To the residue 50ml of hexane : diethyl ether = 4:1 is added and the resulting suspension is stirred for 5 minutes. 20g of the title compound are obtained after filtration of the mixture as a brown crystalline solid.

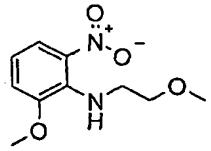
b) 2-Chloro-1-methoxy-3-nitro-benzene:



To a mixture consisting of 15.5g (92.26mmol) 2-methoxy-6-nitro-phenylamine, 31ml water and 31ml conc. HCl, a solution of 6.36g (92.26mmol) $NaNO_2$ in 38ml water is slowly added dropwise at -10°C - 0°C. After stirring for 0.5h the mixture is slowly added to a solution of 11.88g (120mmol) CuCl in 93ml conc. HCl. After completion of the addition stirring is continued for 1.5h at room temperature and for 0.5h at reflux temperature. The reaction

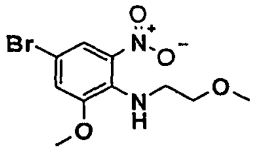
mixture is allowed to cool to room temperature and is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 12.6g of the title compound as a crystalline solid.

c) (2-Methoxy-ethyl)-(2-methoxy-6-nitro-phenyl)-amine:



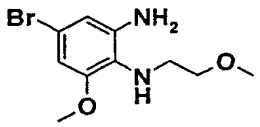
A mixture of 7.5g (40mmol) 2-chloro-1-methoxy-3-nitro-benzene, 14ml diisopropylethylamine and 35ml 2-methoxyethyl amine is heated (180°C oil bath temperature) in a closed steel reactor for 25 min. Then the reaction mixture is cooled to room temperature and is concentrated in vacuo (3 x coevaporation with toluene) to obtain ca. 20g (which contains 85% of the title compound) of a red oil which is used without further purification in the next step.

d) (4-Bromo-2-methoxy-6-nitro-phenyl)-(2-methoxy-ethyl)-amine



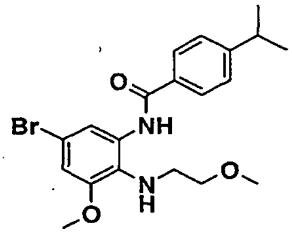
To a solution of ca. 20 g (contains 15.65g , 58.9 mmol) (2-methoxy-ethyl)-(2-methoxy-6-nitro-phenyl)-amine in 150ml glacial acetic acid, 3.0ml (58.9mmol) bromine is slowly added at room temperature. The reaction mixture is stirred at room temperature for 3h. 600ml EtOAc are added and this solution is washed with 4n NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is recrystallized from diethyl ether/hexane to afford 13g of the pure title compound as orange crystals and 6.6g of an orange oil which contained 50% of the starting material.

e) 5-Bromo-3-methoxy-N*2*-(2-methoxy-ethyl)-benzene-1,2-diamine



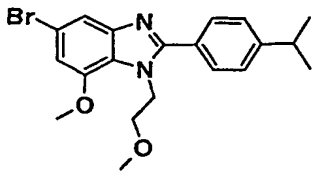
A solution of 6.1g (20mmol) (4-bromo-2-methoxy-6-nitro-phenyl)-(2-methoxy-ethyl)-amine in 140ml THF is hydrogenated in the presence of 1.4g Raney-Nickel (B113W Degussa) at normal pressure for 25h. The catalyst is filtered off and the filtrate is concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 4.95g of the title compound as a as a reddish oil.

f) N-[5-Bromo-3-methoxy-2-(2-methoxy-ethylamino)-phenyl]-4-isopropyl-benzamide



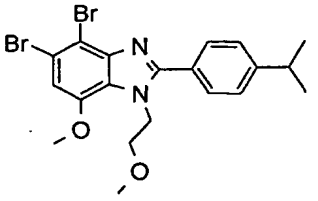
A solution of 4.95g (18mmol) 5-bromo-3-methoxy-N*2*-(2-methoxy-ethyl)-benzene-1,2-diamine, 5.15g (27mmol) EDC, 3.3g (27mmol) 4-dimethylamino-pyridine and 2.94g (18mmol) 4-isopropyl benzoic acid in 150ml dichloromethane is stirred at room temperature for 14h. After that 400ml EtOAc are added and the organic phase washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 7.48g of the title compound as a reddish oil.

g) 5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



A solution of 748mg (1.77mmol) N-[5-bromo-3-methoxy-2-(2-methoxy-ethylamino)-phenyl]-4-isopropyl-benzamide in 10ml AcOH is stirred at 100°C for 2h. The reaction mixture is cooled to room temperature 200ml ethyl acetate is added. The solution is washed with 4N NaOH (2x) and with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 625mg of the title compound as a colorless solid.

Example 23: 4,5-Dibromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

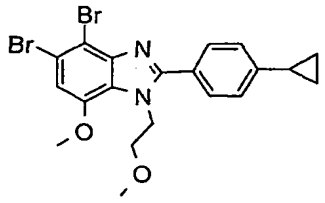


To a solution of 403mg (1.0 mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 8ml glacial acetic acid, 240mg (1.5mmol) bromine is slowly added at 10°C. The reaction mixture is allowed to warm to room temperature and is stirred for 3h. 250ml EtOAc are added and this solution is washed 1n NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is recrystallized from EtOAc/hexane to afford 30mg of the title compound as colorless crystals.

R_f = 0.23 (hexane/EtOAc = 3:1)

MS: 481 $(M+1)^+$ (2x ^{79}Br), 483 $(M+1)^+$ (^{79}Br, ^{81}Br), 485 $(M+1)^+$ (2x ^{81}Br)

Example 24: 4,5-Dibromo-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



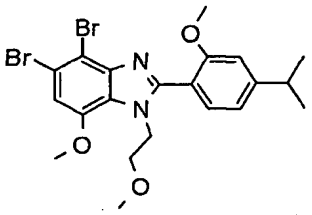
The compound is prepared as described in example 23 by using 4-cyclpropyl-benzoic acid instead of 4-isopropyl-benzoic acid.

R_t = 2.455min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 479 $(M+1)^+$ (2x ^{79}Br), 481 $(M+1)^+$ (^{79}Br, ^{81}Br), 483 $(M+1)^+$ (2x ^{81}Br)

Using the methods described for the preparation of examples 1 and 23 the following compound can be prepared (using 2-methoxy-4-isopropyl-benzoic acid in the appropriate step):

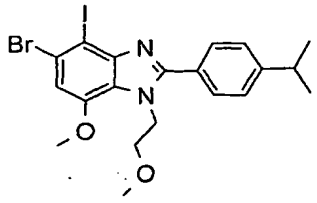
Example 25: 4,5-Dibromo-2-(4-isopropyl-2-methoxy-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.34min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 511 $(M+1)^+$ (2x ^{79}Br), 513 $(M+1)^+$ (^{79}Br, ^{81}Br), 515 $(M+1)^+$ (2x ^{81}Br)

Example 26: 4-Iodo-5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



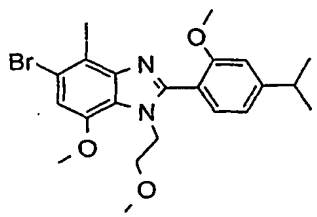
A solution of 100mg (0.248mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole and 61mg (0.273mmol) N-iodosuccinimide in 3ml acetonitrile is refluxed for 12h. The reaction mixture is cooled to room temperature and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) and recrystallisation from hexane/diethyl ether afforded 82mg of the title compound as colorless crystals.

R_t = 2.60min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 529 $(M+1)^+$ (^{79}Br), 531 $(M+1)^+$ (^{81}Br)

Using the methods described for the preparation of examples 1 and 26 the following compound can be prepared (using 2-methoxy-4-isopropyl-benzoic acid in the appropriate step):

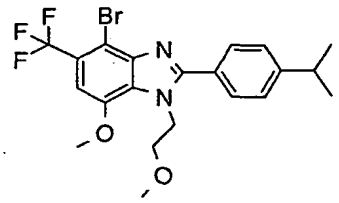
Example 27: 5-Bromo-4-iodo-2-(4-isopropyl-2-methoxy-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.38min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 559 $(M+1)^+$ (^{79}Br), 561 $(M+1)^+$ (^{81}Br)

Example 28: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-trifluoromethyl-1H-benzoimidazole

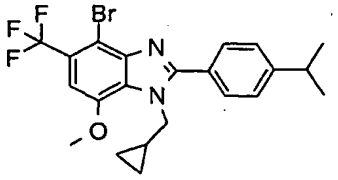


The title compound and the precursors can be prepared using the same synthesis sequence as described in example 1 and 23 from 5-trifluoromethyl-3-methoxy-benzene-1,2-diamine.

R_t = 2.73min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 471 $(M+1)^+$ (^{79}Br), 473 $(M+1)^+$ (^{81}Br)

Example 29: 4-Bromo-1-cyclopropylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-5-trifluoromethyl-1H-benzoimidazole



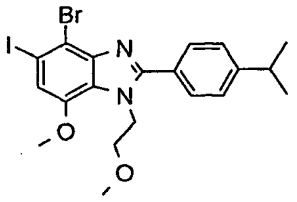
The title compound can be prepared using the same synthesis sequence as described in example 28 by using bromo-methyl-cyclopropane instead of 1-bromo-2-methoxy-ethane.

R_t = 2.79min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 467 $(M+1)^+$ (^{79}Br), 469 $(M+1)^+$ (^{81}Br)

a) 5-Trifluoro-3-methoxy-benzene-1,2-diamine can be prepared starting from 1-methoxy-3-nitro-5-trifluoromethyl-benzene using the same reaction sequence as described for the preparation of 3-bromo-6-methoxy-benzene-1,2-diamine as described in example 1 (steps c and d).

Example 30: 4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



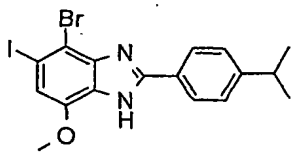
The title compound is prepared starting from 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole using the same reaction conditions as described for the preparation of example 1.

R_t = 2.52min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 529$(M+1)^+$ (^{79}Br), 531$(M+1)^+$ (^{81}Br)

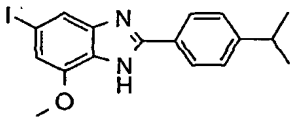
The starting material can be prepared as follows:

a) 4-Bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole:

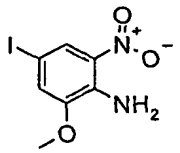


To a solution of 200mg (0.51mmol) 5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole in 3ml glacial acetic acid is slowly added 82mg (0.51mmol) bromine. The reaction mixture is stirred for 45min. 30ml EtOAc are added and this solution is washed 2n NaOH, water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) and recrystallized from EtOAc/diethyl ether to afford 126mg of the title compound as off-white crystals.

b) 5-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole is prepared starting from 4-iodo-2-methoxy-6-nitro-phenylamine using the same reaction sequence as described in examples 1 and 23.

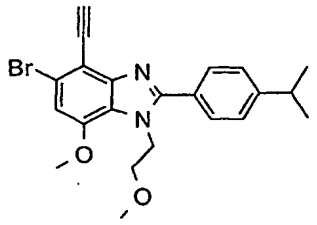


c) 4-Iodo-2-methoxy-6-nitro-phenylamine:



A mixture of 6.2g (36.9mmol) 2-methoxy-6-nitro-phenylamine, 9.4g (37mmol) iodine and 5.8g (18.5mmol) silver sulfate in 90ml glacial acetic acid is stirred at 60°C for 12h. The reaction mixture is cooled to room temperature, poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 8.57g of the title compound as bright red crystals.

Example 31: 5-Bromo-4-ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

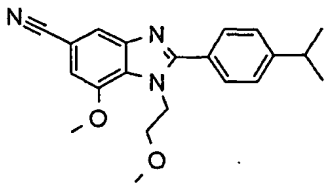


The title compound is prepared starting from 5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole using the same methodology as described for the preparation of example 11.

R_t = 2.24min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 427$(M+1)^+$ (^{79}Br), 429$(M+1)^+$ (^{81}Br)

Example 32: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

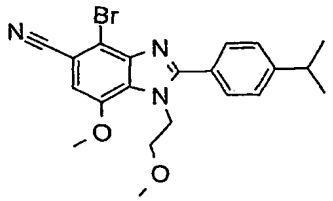


A mixture of 430mg (1.07mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 22), 125mg (1.07mmol) zinc cyanide and 20mg tetrakis(triphenylphosphine) palladium in 5ml DMF is heated in a microwave oven for 75min (180°C). After that the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (3x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 250mg of the title compound as a colorless solid.

R_t = 2.27min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 350 $(M+1)^+$

Example 33: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

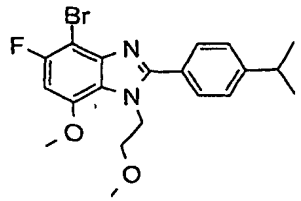


A mixture of 110mg (0.315mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile and 56mg (0.315mmol) N-bromosuccinimide in 5ml acetonitrile is stirred at reflux for 3h. Then the solvents are evaporated and the residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) and recrystallized from EtOAc/diethyl ether/hexane to afford 60mg of the title compound as colorless crystals.

R_t = 2.59min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 428 $(M+1)^+$ (^{79}Br), 430 $(M+1)^+$ (^{81}Br)

Example 34: 4-Bromo-5-fluoro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

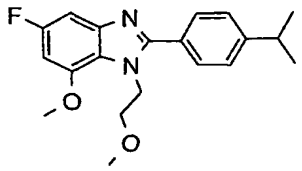


The title compound is prepared from 4-bromo-5-fluoro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole using the method described in example 1

R_t = 2.30min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

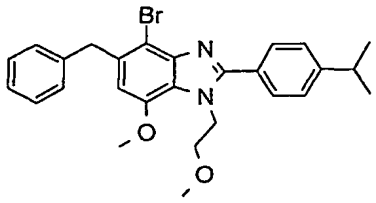
MS: 421 $(M+1)^+$ (^{79}Br), 423 $(M+1)^+$ (^{81}Br)

Preparation of the starting material 5-fluoro-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole:



To a solution of 400mg (0.98mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 3ml dry THF, n-BuLi (0.740ml, 1.18mmol) is added slowly at -78°C. After stirring for 45min. at -78°C N-fluoro-bis(phenylsulfonyl)amine (568.7mg, 1.77mmol) is added. Stirring at -78°C is continued for another hour and then the reaction mixture is warmed to room temperature. After that the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (3x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1 -> 1:1) to afford 40mg of the title compound as a colorless oil.

Example 35: 5-Benzyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



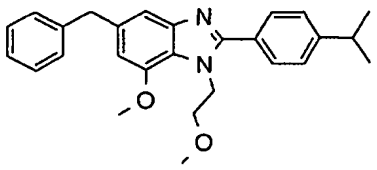
6µl (0.122mmol) bromine are added to a solution of 48mg (0.116mmol) 5-benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 6ml glacial acetic acid. The reaction mixture is stirred at room temperature for 10min. 25ml EtOAc are added and this solution is washed 4N NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is recrystallized from dichloromethane/diethyl ether/hexane to afford 40mg of the title compound as colorless crystals.

R_t = 2.38min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 493 $(M+1)^+$ (^{79}Br), 495 $(M+1)^+$ (^{81}Br)

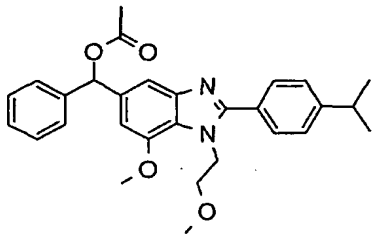
The starting materials can be prepared as follows:

a) 5-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



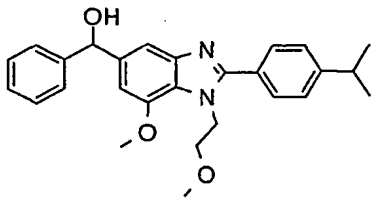
A solution of 150mg (0.317mmol) acetic acid[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methyl ester in 8ml THF:MeOH = 1:2 is hydrogenated in the presence of 50mg Pd/C (Engelhard 4505). Then the catalyst is filtered off and the filtrate is concentrated in vacuo to afford 120mg of the title compound as a colorless oil.

b) Acetic acid[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methyl ester



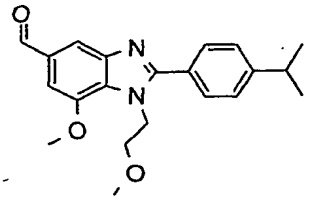
A solution of 136mg (0.30mmol) [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methanol, 46µl (0.66mmol) acetyl chloride and 125µl (0.90mmol) triethylamine in 3 ml dichloromethane is stirred at room temperature for 1h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 140mg of the title compound as a colorless oil.

c) [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenyl-methanol



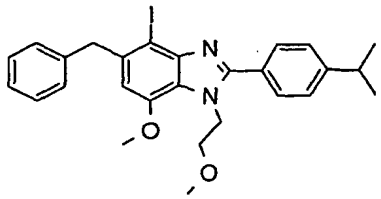
A solution of 150mg (0.426mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde in 2ml THF is treated with excess phenylmagnesiumbromide (prepared from 112µl bromobenzene and 26mg magnesium in 5ml diethyl ether). The resulting mixture is stirred at room temperature for 1h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:2) to afford 136mg of the title compound as a white solid.

d) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde



A mixture of 480mg (1.37mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile (example 32) , 15mg Raney-Nickel (in water), 967mg (11.0mmol) sodium hypophosphite (in 10ml water), 10ml acetic acid and 20ml pyridine is stirred for 6h at 60°C. The catalyst is filtered off and the filtrate is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 330mg of the title compound as a white crystalline solid.

Example 36: 5-Benzyl-4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

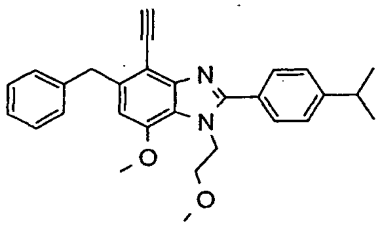


417mg (1.78 mmol) N-iodo-succinimide are added to a solution of 670mg (1.62mmol) 5-benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 25ml acetonitrile. The reaction mixture is stirred at reflux temperature for 3h. The reaction mixture is poured on water and extracted (3X) with ethyl acetate. The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 4:1) to afford 582mg of the title compound as a white crystalline solid.

R_t = 2.39min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 541 $(M+1)^+$

Example 37: 5-Benzyl-4-ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

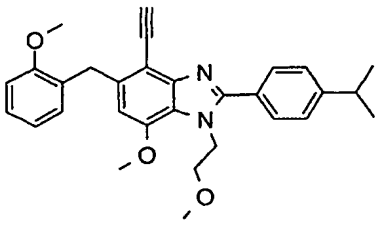


The title compound is prepared starting from 5-benzyl-4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole using the same methodology as described for the preparation of example 11.

R_t = 2.27min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 439 $(M+1)^+$

Example 38: 4-Ethynyl-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

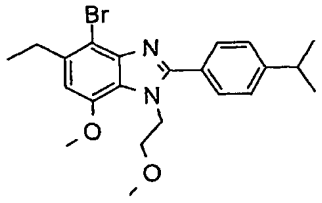


The title compound is prepared starting from 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole using the same methodology as described for the preparation of example 11.

R_t = 2.26 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 469 $(M+1)^+$

Example 39: 4-Bromo-5-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

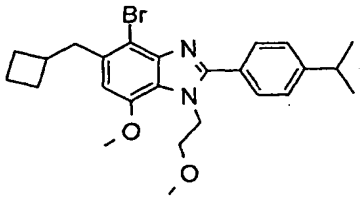


The title compound is prepared using the same methodology as described for the preparation of example 35. (Instead of phenylmagnesiumbromide, ethylmagnesiumbromide is used.)

R_t = 2.24min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 431 $(M+1)^+$ (^{79}Br), 433 $(M+1)^+$ (^{81}Br)

Example 40: 4-Bromo-5-cyclobutylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

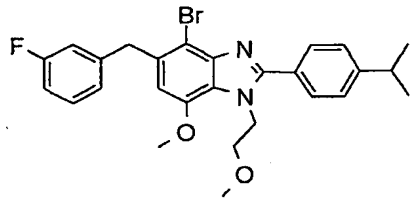


The title compound is prepared using the same methodology as described for the preparation of example 35. (Instead of phenylmagnesiumbromide, cyclobutyl-methylmagnesiumbromide is used.)

R_t = 2.53min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 471 $(M+1)^+$ (^{79}Br), 473 $(M+1)^+$ (^{81}Br)

Example 41: 4-Bromo-5-(3-fluoro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

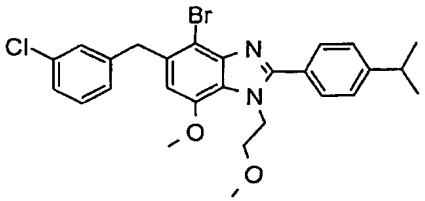


The title compound is prepared using the same methodology as described for the preparation of example 35. (Instead of phenylmagnesiumbromide, 3-fluoro-phenylmagnesiumbromide is used.)

R_t = 2.43min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 511 $(M+1)^+$ (^{79}Br), 513 $(M+1)^+$ (^{81}Br)

Example 42: 4-Bromo-5-(3-chloro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

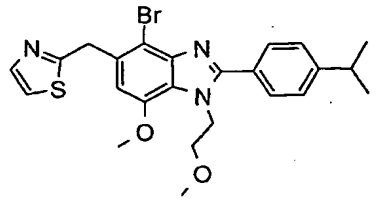


The title compound is prepared using the same methodology as described for the preparation of example 35. (Instead of phenylmagnesiumbromide, 3-chloro-phenylmagnesiumbromide is used.)

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 527 $(M+1)^+$ (^{35}Cl,^{79}Br), 529 $(M+1)^+$ (^{35}Cl, ^{81}Br / ^{37}Cl, ^{79}Br), 531 $(M+1)^+$ (^{37}Cl,^{81}Br)

Example 43: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-thiazol-2-ylmethyl-1H-benzoimidazole

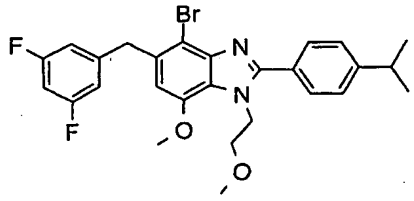


The title compound is prepared using the same methodology as described for the preparation of example 35. Instead of phenylmagnesiumbromide, 2-lithio-thiazole (prepared from 2-bromo-thiazole and n-BuLi) is used.

R_t = 2.14min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 500 $(M+1)^+$ (^{79}Br), 502 $(M+1)^+$ (^{81}Br)

Example 44: 4-Bromo-5-(3,5-difluoro-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

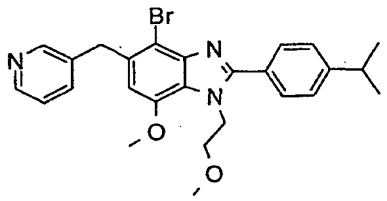


The title compound is prepared using the same methodology as described for the preparation of example 35. Instead of phenylmagnesiumbromide, 3,5-difluoro-phenylmagnesiumbromide is used.

R_t = 2.40min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 529 $(M+1)^+$ (^{79}Br), 531$(M+1)^+$ (^{81}Br)

Example 45: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-ylmethyl-1H-benzoimidazole

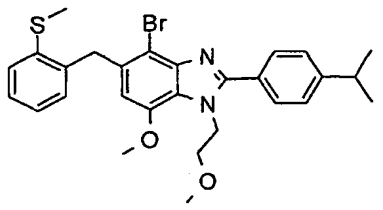


The title compound is prepared using the same methodology as described for the preparation of example 35. Instead of phenylmagnesiumbromide, 3-lithio-pyridine (prepared from 3-bromo-pyridine and n-BuLi) is used.

R_t = 1.89min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 494 $(M+1)^+$ (^{79}Br), 496 $(M+1)^+$ (^{81}Br)

Example 46: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzyl)-1H-benzoimidazole



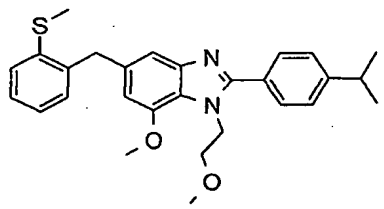
The title compound is prepared using the same methodology as described for the preparation of example 35.

R_t = 2.388min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 539 $(M+1)^+$ (^{79}Br), 541 $(M+1)^+$ (^{81}Br)

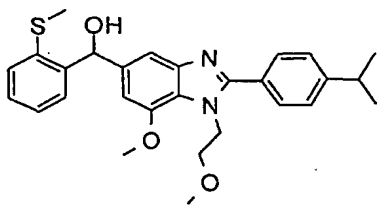
The starting material can be prepared as follows:

a) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzyl)-1H-benzoimidazole



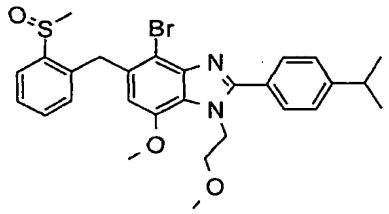
To a mixture of 797mg (1.67mmol) [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methylsulfanyl-phenyl)-methanol, 436mg iodine in 13ml acetic acid (100%), 0.88ml of phosphinic acid (ca. 5 equiv.) is added at room temperature. The mixture is heated to 60°C and stirred for 1h. After that the reaction mixture is allowed to cool to room temperature and 100ml ethyl acetate is added. The combined organic layers are washed with 4N NaOH-solution (4x), water (2x) and brine, dried over $MgSO_4$, filtered and the filtrate is concentrated in vacuo to afford 914mg of the title compound as a colorless oil.

b) [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methylsulfanyl-phenyl)-methanol



The title compound is prepared using the same methodology as described for the preparation of example 35 (step c). Instead of phenylmagnesiumbromide, 1-bromo-magnesium-2-methylsulfanyl-benzene (prepared from 1-bromo-2-methylsulfanyl-benzene and magnesium) is used.

Example 47: 4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



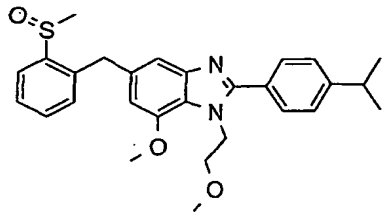
53µl (0.122mmol) bromine are added to a solution of 496mg (1.03mmol) 2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole in 22ml glacial acetic acid. The reaction mixture is stirred at room temperature for 10min. Then 25ml EtOAc are added and this solution is washed with 4N NaOH (2x), water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:4) to afford 340mg of the title compound as colorless crystals.

R_t = 2.12min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 555 $(M+1)^+$ (^{79}Br), 557 $(M+1)^+$ (^{81}Br)

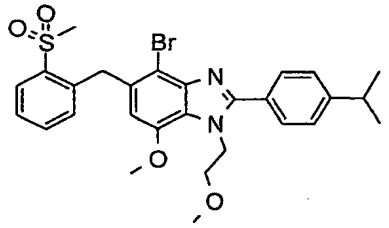
The starting material can be prepared as follows:

a): 2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



A mixture of 714mg (1.32mmol) of 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzyl)-1H-benzoimidazole and 142µl (1.39mmol) hydrogen peroxide solution (30%) in 13ml acetic acid is stirred at room temperature for 1.5 h. After that 25ml EtOAc are added and this solution is washed with 4n NaOH (2x), water and sodiumhydrogensulfite solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (EtOAc) to afford 496mg of the title compound as colorless crystals.

Example 48: 4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfonyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

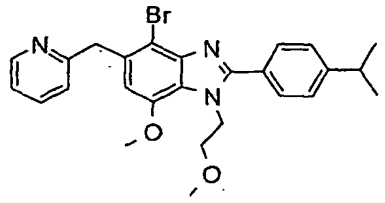


A mixture of 140mg (0.252mmol) of 4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole and 30µl (0.265mmol) hydrogen peroxide solution (30%) in 3ml acetic acid is stirred at reflux temperature for 3 h. After that the reaction mixture is allowed to cool to room temperature and 25ml EtOAc are added and this solution is washed with 4n NaOH (2x), water and sodiumhydrogensulfite solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 112mg of the title compound as pale red crystals.

R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 571 $(M+1)^+$ (^{79}Br), 573 $(M+1)^+$ (^{81}Br)

Example 49: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-2-ylmethyl-1H-benzoimidazole



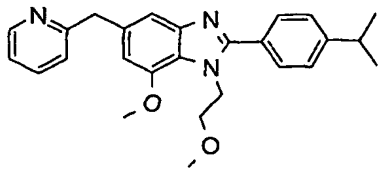
The title compound is prepared using the same methodology as described for the preparation of example 35.

R_t = 1.90 *min* (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 494 $(M+1)^+$ (^{79}Br), 496 $(M+1)^+$ (^{81}Br)

The starting material can be prepared as follows:

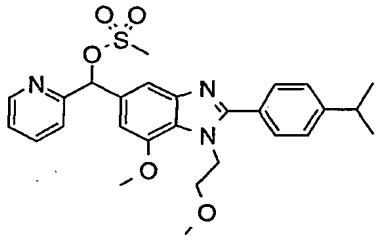
a) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-2-ylmethyl-1H-benzoimidazole



To a solution of ca. 250mg of methanesulfonic acid [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-pyridin-2-yl-methyl ester in 7ml THF, 50mg $LiAlH_4$ are added. The mixture is heated to reflux temperature and stirred for 3h. After that the reaction mixture is allowed to cool to room temperature and 1N NaOH solution is added and this

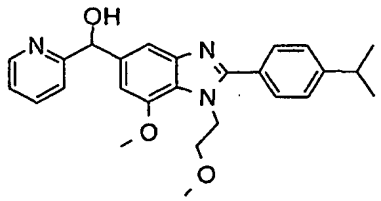
mixture is stirred for 30min and filtered. The filtrate is extracted with ethyl acetate (3x). The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and the filtrate is concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (CH_2Cl_2:MeOH = 95:5) to afford 40mg of the title compound as an oil.

b) Methanesulfonic acid [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-pyridin-2-yl-methyl ester



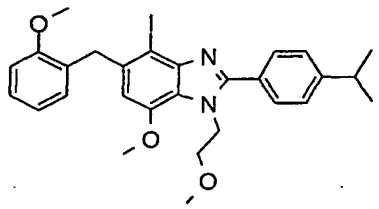
A mixture of 330mg (0.76mmol) [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-pyridin-2-yl-methanol, 0.6ml ethyl-diisopropyl-amine and 0.25ml methanesulfonyl chloride is stirred at 0°C for 1h. Then the reaction mixture is poured on water and extracted (3X) with ethyl acetate. The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the title product as an oil that is used directly in the next step.

c) [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-pyridin-2-yl-methanol



The title compound is prepared using the same methodology as described for the preparation of example 35 (step c). Instead of phenylmagnesiumbromide, 2-lithio-pyridine (prepared from 2-bromo-pyridine and n-BuLi) is used.

Example 50: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole



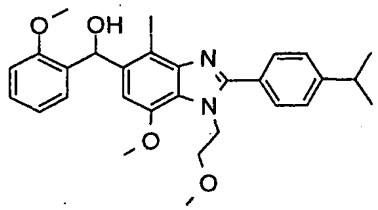
The title compound is prepared starting from [4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanol using the same methodology as described for the preparation of example 46 (step a).

R_t = 2.37 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 571 $(M+1)^+$

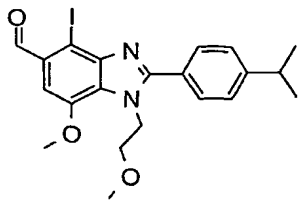
The starting material can be prepared as follows:

[4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanol



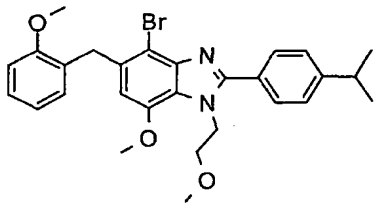
The title compound is prepared from 4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde and 2-methoxyphenyl-magnesium bromide as described in example 35.

4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde



The title compound is prepared from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde (preparation see example 35) as described in example 59.

Example 51: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

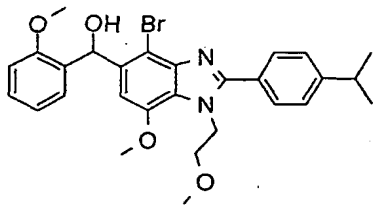


The title compound is prepared starting from [4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanol using the same methodology as described for the preparation of example 46 (step a).

R_t = 2.35 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)
MS: 523 $(M+1)^+$ (^{79}Br), 525 $(M+1)^+$ (^{81}Br)

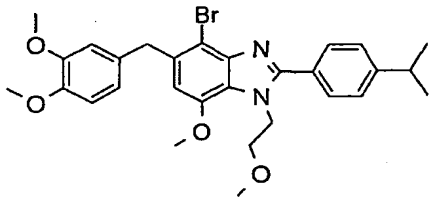
The starting material can be prepared as follows:

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanol



The title compound is prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde (see example 41, step c) and 2-methoxyphenyl-magnesium bromide as described in example 35.

Example 52: 4-Bromo-5-(3,4-dimethoxy-benzyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

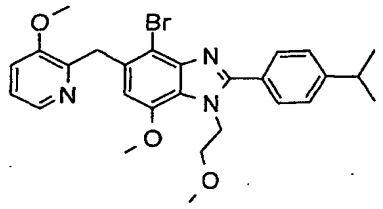


The title compound is prepared using the same methodology as described for the preparation of example 35. Instead of phenylmagnesiumbromide, 3,4-dimethoxyphenyl-magnesium-bromide is used.

R_t = 2.26 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 553 $(M+1)^+$ (^{79}Br), 555 $(M+1)^+$ (^{81}Br)

Example 53: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-pyridin-2-ylmethyl)-1H-benzoimidazole

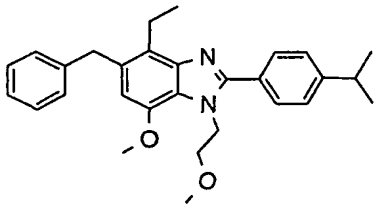


The title compound is prepared using the same methodology as described for the preparation of example 35. Instead of phenylmagnesiumbromide, 2-lithium-3-methoxy-pyridine is used.

R_t = 1.94 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 524 $(M+1)^+$ (^{79}Br), 526 $(M+1)^+$ (^{81}Br)

Example 54: 5-Benzyl-4-ethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



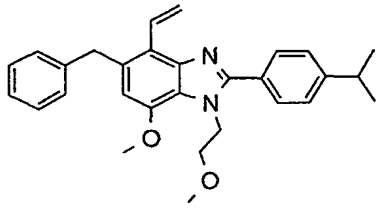
A solution of 58mg (0.13mmol) 5-benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-vinyl-1H-benzoimidazole in 5ml methanol is hydrogenated in the presence of 10mg Raney-Nickel (B113W Degussa) at normal pressure for 25h. The catalyst is filtered off and the filtrate is concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 6:1) to afford 26mg of the title compound as a white crystalline solid.

R_t = 2.29 in (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 443 $(M+1)^+$

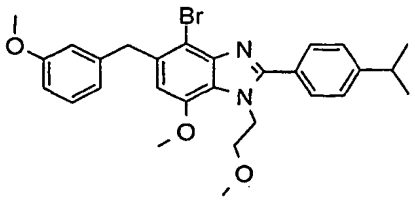
The starting material can be prepared as follows:

5-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-vinyl-1H-benzoimidazole



A mixture of 300mg (0.556mmol) 5-benzyl-4-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole, 40mg bis(triphenylphosphine) palladium (II) dichloride and 0.2ml tributyl(vinyl)stannane in 3ml THF is stirred at reflux temperature for 24h. The reaction mixture is concentrated in vacuo and the residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 6:1) to afford 278mg of the title compound as a yellow crystalline solid.

Example 55: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(3-methoxy-benzyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole



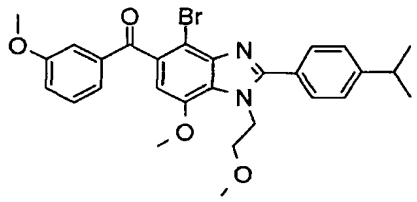
A mixture of 125mg (0.233mmol) [4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(3-methoxy-phenyl)-methanone (example 26o), 45mg KOH pellets, 3.2ml hydrazine-monohydrate, 0.5ml water and 13ml ethyleneglykol is stirred at

190°C for 2h. After that the reaction mixture is poured on 4N HCl-solution and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 20mg of the title compound as an off-white crystalline solid.

R_t = 2.33 in (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 523 $(M+1)^+$ (^{79}Br), 525 $(M+1)^+$ (^{81}Br)

Example 56: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(3-methoxy-phenyl)-methanone



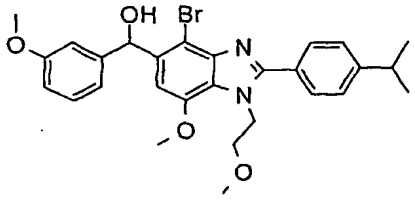
To a solution of 0.16ml oxalylchloride in 4ml dichloromethane, 0.27ml DMSO (in 0.8ml dichloromethane is slowly added at -60°C. This mixture is stirred under argon at -60°C for 0.5h. Then 250mg (0.463mmol) [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(3-methoxy-phenyl)-methanol (in 2ml dichloromethane) are added and stirring is continued at -60°C for 1h. 1ml triethylamine is added and the reaction mixture is allowed to warm to room temperature, poured on water and extracted (3x) with dichloromethane. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 179mg of the title compound as a colorless oil.

R_t = 2.47 in (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 537 $(M+1)^+$ (^{79}Br), 539 $(M+1)^+$ (^{81}Br)

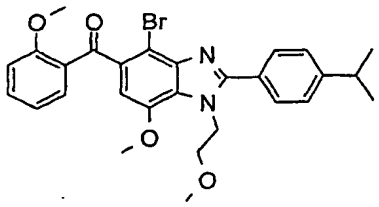
The starting material can be prepared as follows:

[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(3-methoxy-phenyl)-methanol



The title compound is prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde and 3-methoxyphenyl-magnesium bromide as described in examples 35 and 51.

Example 57: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-(2-methoxy-phenyl)-methanone

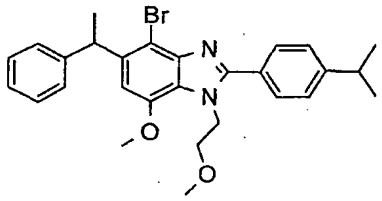


The title compound can be prepared as described in example 56, using 2-methoxyphenyl magnesium bromide instead of 3-methoxy-phenylmagnesium bromide.

R_t = 2.37 in (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 537 $(M+1)^+$ (^{79}Br), 539 $(M+1)^+$ (^{81}Br)

Example 58: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(1-phenyl-ethyl)-1H-benzoimidazole:



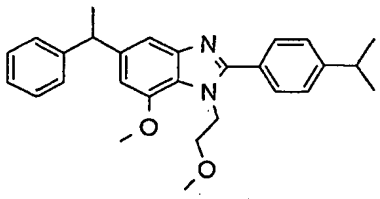
The title compound is prepared from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(1-phenyl-ethyl)-1H-benzoimidazole using the methodology described in example 35.

R_t = 2.39 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 507 $(M+1)^+$ (^{79}Br), 509 $(M+1)^+$ (^{81}Br)

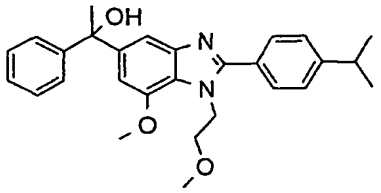
The starting materials can be prepared as follows:

a) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(1-phenyl-ethyl)-1H-benzoimidazole:



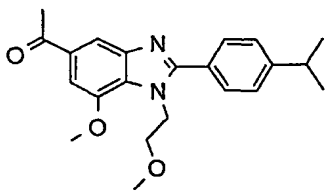
The title compound is prepared from 1-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-1-phenyl-ethanol using the methodology described in example 46 (step a).

b) 1-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-1-phenyl-ethanol:



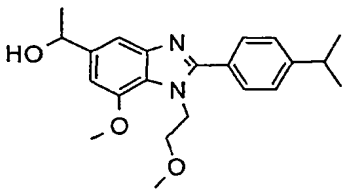
A solution of 163mg (0.445mmol) 1-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-ethanone in 2ml THF is treated with excess phenylmagnesiumbromide (prepared from 112µl bromobenzene and 26mg magnesium in 5ml diethyl ether). The resulting mixture is stirred at room temperature for 1h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 109mg of the title compound as an oil.

c) 1-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-ethanone:



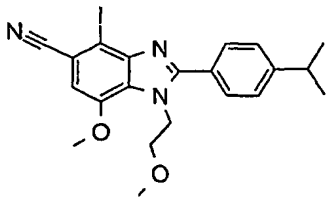
To a solution of 0.17ml oxalylchloride in 4ml dichloromethane, 0.285ml DMSO (in 0.8ml dichloromethane is slowly added at -60°C. This mixture is stirred under argon at -60°C for 0.5h. Then 180mg (0.488mmol) 1-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-ethanol (in 2ml dichloromethane) are added and stirring is continued at -60°C for 1h. 1ml triethylamine is added and the reaction mixture is allowed to warm to room temperature, poured on water and extracted (3x) with dichloromethane. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 163mg of the title compound as a colorless oil.

d) 1-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-ethanol:



A solution of 150mg (0.426mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde in 2ml THF is treated with excess methylmagnesiumiodide (prepared from 207mg methyliodide and 35mg magnesium in 5ml diethyl ether). The resulting mixture is stirred at room temperature for 1h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 180mg of the title compound as an oil.

Example 59: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile

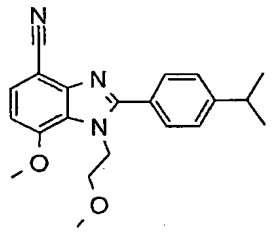


A mixture of 50mg (0.143mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile and 36mg (0.143mmol) iodine and 22mg (0.072mmol) silver sulfate in 1ml acetic acid is stirred at reflux for 3h. Then the filtrate is poured on 2N NaOH and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 10mg of the title compound as a white crystalline solid.

R_t = 2.64min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 476 $(M+1)^+$

Example 60: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile



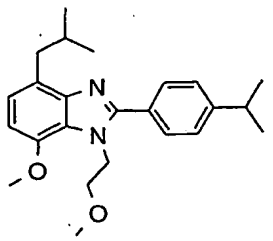
The title compound is prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 1) using the same methodology as described for the preparation of example 32.

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 350 $(M+1)^+$

Starting from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-4-carbonitrile (example 60) the following compounds can be prepared using the same reaction sequence as described for the preparation of example 35:

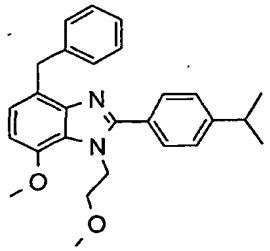
Example 61: 4-Isobutyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.16min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 381 $(M+1)^+$

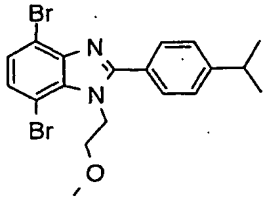
Example 62: 4-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.23min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 415 $(M+1)^+$

Example 63: 4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

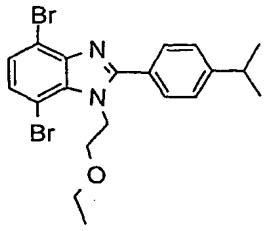


R_t = 2.73min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 451 $(M+1)^+$ (2x ^{79}Br), 453 $(M+1)^+$ (^{79}Br, ^{81}Br), 455 $(M+1)^+$ (2x ^{81}Br)

The title compound and the precursors are prepared from 3,6-Dibromo-benzene-1,2-diamine [Naef, R.; Balli, H. *Helvetica Chimica Acta* **1978**, *61*(8), 2958-73] using the same methodology as described for the preparation of example 1.

Example 64: 4,7-Dibromo-2-(4-isopropyl-phenyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole

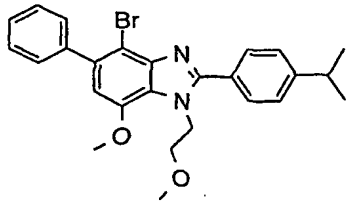


R_t = 2.82min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 465 $(M+1)^+$ (2x ^{79}Br), 467 $(M+1)^+$ (^{79}Br, ^{81}Br), 469 $(M+1)^+$ (2x ^{81}Br)

The title compound is prepared using the same methodology as described for the preparation of example 63.

Example 65: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenyl-1H-benzoimidazole



A mixture of 150mg (0.283mmol) 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 30), 38mg (0.312mmol) phenylboronic acid, 60mg (0.567mmol) sodium carbonate and 16mg (0.014mmol)

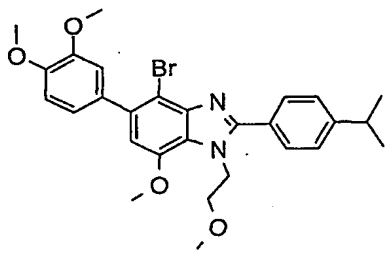
tetrakis(triphenylphosphine)palladium in 6ml toluene/water (3:1) is stirred at 100°C for 12h. Then the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 3:1) to afford 40mg of the title compound as a white solid.

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 479 $(M+1)^+$ (^{79}Br), 481 $(M+1)^+$ (^{81}Br)

Using the same methodology as described in example 65 the following compounds are prepared from the corresponding boronic acids:

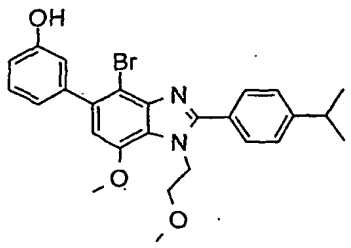
Example 66: 4-Bromo-5-(3,4-dimethoxy-phenyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.31min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 539 $(M+1)^+$ (^{79}Br), 541 $(M+1)^+$ (^{81}Br)

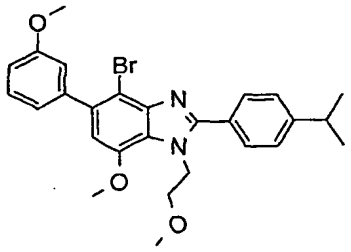
Example 67: 3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-phenol



R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 495 $(M+1)^+$ (^{79}Br), 497 $(M+1)^+$ (^{81}Br)

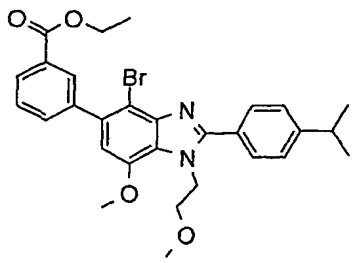
Example 68: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole



R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 509 $(M+1)^+$ (^{79}Br), 511 $(M+1)^+$ (^{81}Br)

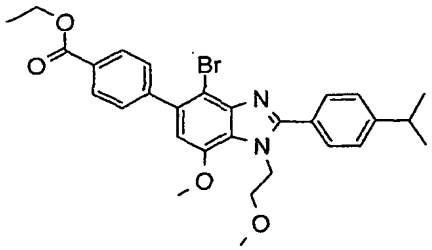
Example 69: 3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester



R_t = 2.50min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

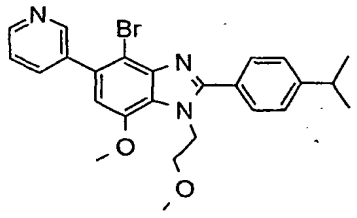
Example 70: 4-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzoic acid ethyl ester



R_t = 2.51min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

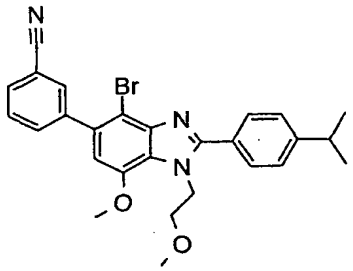
Example 71: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-3-yl-1H-benzoimidazole



R_t = 2.00min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 480 $(M+1)^+$ (^{79}Br), 482 $(M+1)^+$ (^{81}Br)

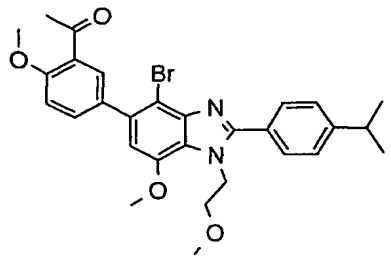
Example 72: 3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzonitrile



R_t = 2.38min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 504 $(M+1)^+$ (^{79}Br), 506 $(M+1)^+$ (^{81}Br)

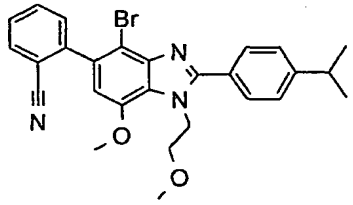
Example 73: 1-{5-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-2-methoxy-phenyl}-ethanone



R_t = 2.305min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

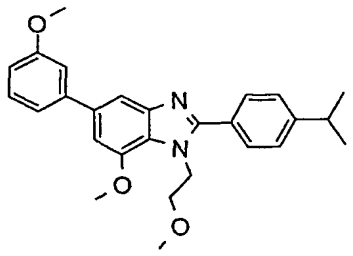
Example 74: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-benzonitrile



R_t = 2.35min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 504 $(M+1)^+$ (^{79}Br), 506 $(M+1)^+$ (^{81}Br)

Example 75: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(3-methoxy-phenyl)-1H-benzoimidazole

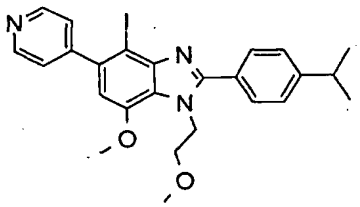


(The title compound is prepared from 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole instead of 4-bromo-5-iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole)

R_t = 2.06min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 417 $(M+1)^+$

Example 76: 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-4-yl-1H-benzoimidazole

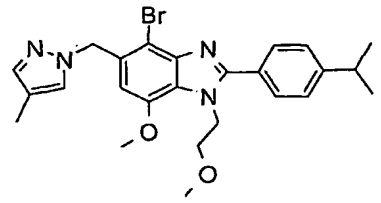


The compound is prepared using the methodology described in Example 40. The product of this reaction, 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-4-yl-1H-benzoimidazole, is iodinated as described in example 59 to afford the product.

R_t = 2.008min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 528 $(M+1)^+$

Example 77: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(4-methyl-pyrazol-1-ylmethyl)-1H-benzoimidazole



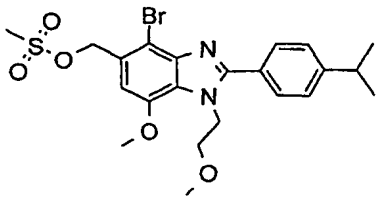
NaH (7mg, 0.3mmol) is added to a solution of 23µl (0.30mmol) 4-methylpyrazole in 2ml DMF. The resulting mixture is stirred at room temperature for 1h, then 119mg (0.23mmol) methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester is added. Stirring is continued for 20h. After that the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (dichloromethane:isopropanol = 95:5) to afford 80mg of the title compound as a white foam.

R_t = 2.28min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 497 $(M+1)^+$ (^{79}Br), 499 $(M+1)^+$ (^{81}Br)

The starting materials can be prepared as follows:

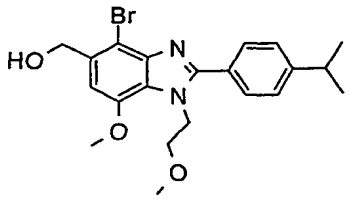
a) Methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester



A mixture of 100mg (0.23mmol) [4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol, 26µl (0.33mmol) methanesufonyl chloride and 60µl

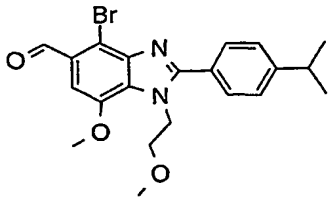
(0.35mmol) diisopropylethylamine in 4ml dichloromethane is stirred at 0°C for 2h. The reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 120mg of the title compound as an oil that is used directly in the next reaction.

b) [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol



$NaBH_4$ (65mg, 1.72mmol) is added to a solution of 370mg (0.858mmol) 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde in 5ml absolute ethanol at 0°C. The reaction mixture is stirred at 0°C for 20min. Then the reaction mixture is poured on water and extracted (3x) with dichloromethane/isopropanol (3:1). The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 380mg of the title compound as a pure crystalline solid.

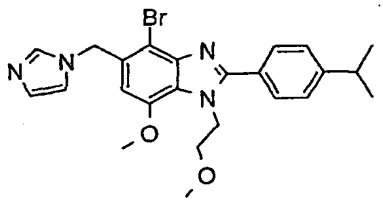
c) 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde



The title compound is prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile (example 33) using the same reaction conditions as described in example 35 step d).

Reaction of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester with either imidazole, 4-bromo-3-methyl-1H-pyrazole, 3,5-dimethyl-1H-pyrazole, 1H-imidazole-2-carboxylic acid ethyl ester, 1H-Imidazole-4-carboxylic acid methyl ester, 3H-imidazo[4,5-b]pyridine, indazole or 5-methyl-2H-tetrazole using the same reaction conditions as described for the preparation of example 77 led to the following compounds:

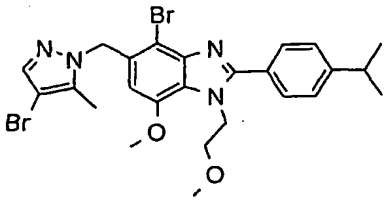
Example 78: 4-Bromo-5-imidazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 1.93min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 483 $(M+1)^+$ (^{79}Br), 485 $(M+1)^+$ (^{81}Br)

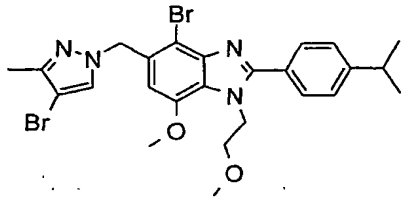
Example 79: 4-Bromo-5-(4-bromo-5-methyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.37min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 575 $(M+1)^+$ (2x ^{79}Br), 577 $(M+1)^+$ (^{79}Br, ^{81}Br), 579 $(M+1)^+$ (2x ^{81}Br)

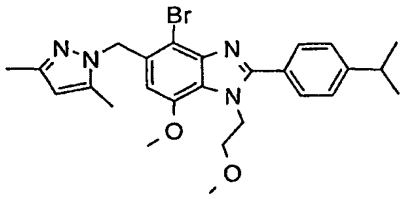
Example 80: 4-Bromo-5-(4-bromo-3-methyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.36min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 575 $(M+1)^+$ (2x ^{79}Br), 577 $(M+1)^+$ (^{79}Br, ^{81}Br), 579 $(M+1)^+$ (2x ^{81}Br)

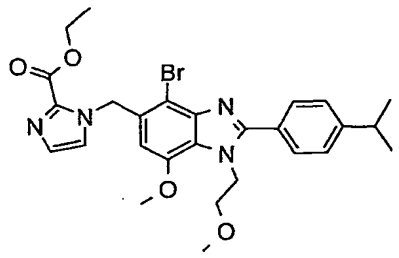
Example 81: 4-Bromo-5-(3,5-dimethyl-pyrazol-1-ylmethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 5.39min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 7min + 0.05% TFA, flow rate 0.5ml/min)

MS: 511 $(M+1)^+$ (^{79}Br), 513 $(M+1)^+$ (^{81}Br)

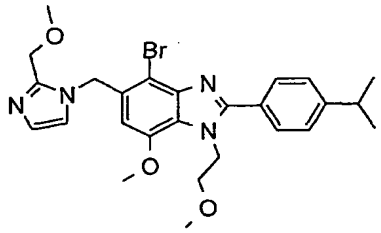
Example 82: 1-[4-Bromo-1-(2-hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid ethyl ester



R_t = 2.08min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 555 $(M+1)^+$ (^{79}Br), 557 $(M+1)^+$ (^{81}Br)

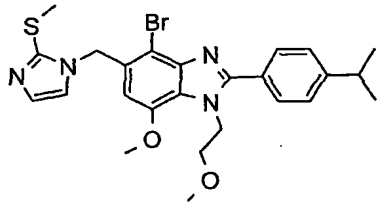
Example 83: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methoxymethyl-imidazol-1-ylmethyl)-1H-benzoimidazole



R_t = 1.96min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 527 $(M+1)^+$ (^{79}Br), 529 $(M+1)^+$ (^{81}Br)

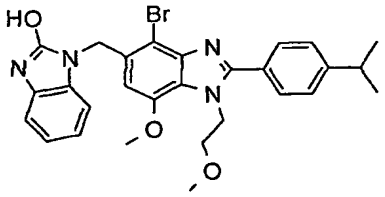
Example 84: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-imidazol-1-ylmethyl)-1H-benzoimidazole



R_t = 1.98min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 529 $(M+1)^+$ (^{79}Br), 531 $(M+1)^+$ (^{81}Br)

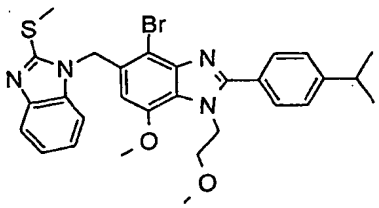
Example 85: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-benzoimidazol-2-ol



R_t = 2.20min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 549 $(M+1)^+$ (^{79}Br), 551 $(M+1)^+$ (^{81}Br)

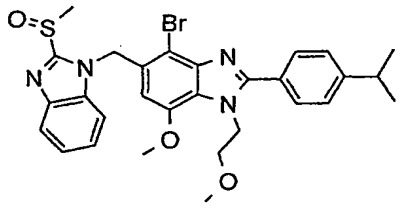
Example 86: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methylsulfanyl-benzoimidazol-1-ylmethyl)-1H-benzoimidazole



R_t = 2.18 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 579 $(M+1)^+$ (^{79}Br), 581 $(M+1)^+$ (^{81}Br)

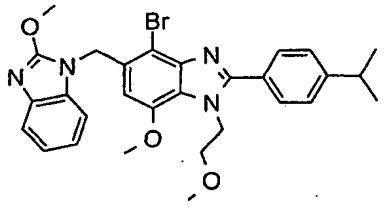
Example 87: 4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfinyl-benzoimidazol-1-ylmethyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.20min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 595 $(M+1)^+$ (^{79}Br), 597 $(M+1)^+$ (^{81}Br)

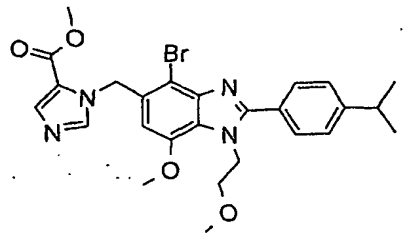
Example 88: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzoimidazol-1-ylmethyl)-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.26min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 563 $(M+1)^+$ (^{79}Br), 565 $(M+1)^+$ (^{81}Br)

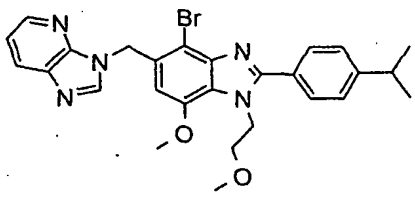
Example 89: 3-[4-Bromo-1-(2-hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazol-5-ylmethyl]-3H-imidazole-4-carboxylic acid methyl ester



R_t = 2.02min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 541 $(M+1)^+$ (^{79}Br), 543 $(M+1)^+$ (^{81}Br)

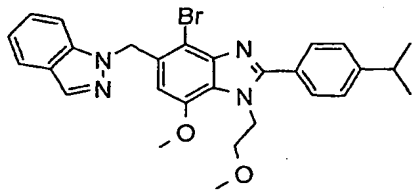
Example 90: 2-[4-Bromo-5-imidazo[4,5-b]pyridin-3-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethanol



R_t = 2.05min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 534 $(M+1)^+$ (^{79}Br), 536 $(M+1)^+$ (^{81}Br)

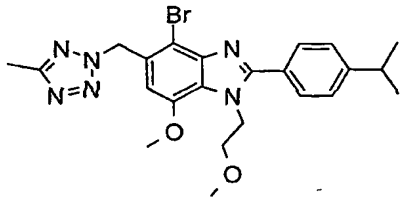
Example 91: 2-[4-Bromo-5-indazol-1-ylmethyl-2-(4-isopropyl-phenyl)-7-methoxy-benzoimidazol-1-yl]-ethanol



R_t = 2.34min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 533 $(M+1)^+$ (^{79}Br), 535 $(M+1)^+$ (^{81}Br)

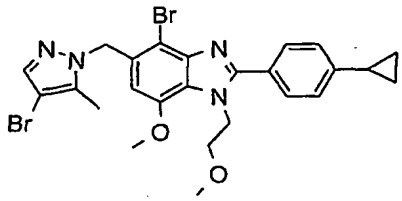
Example 92: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(5-methyl-tetrazol-2-ylmethyl)-benzoimidazol-1-yl]-ethanol



R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 499 $(M+1)^+$ (^{79}Br), 501 $(M+1)^+$ (^{81}Br)

Example 93: 4-Bromo-5-(4-bromo-5-methyl-pyrazol-1-ylmethyl)-2-(4-cyclopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

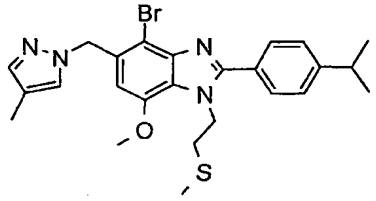


The compound is prepared as described in example 79 by using 4-cyclopropyl-benzoic acid instead of 4-isopropyl-benzoic acid.

R_t = 2.28min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 573 $(M+1)^+$ (2x ^{79}Br), 575 $(M+1)^+$ (^{79}Br, ^{81}Br), 577 $(M+1)^+$ (2x ^{81}Br)

Example 94: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-5-(4-methyl-pyrazol-1-ylmethyl)-1-(2-methylsulfanyl-ethyl)-1H-benzoimidazole

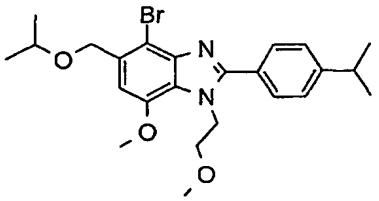


The compound is prepared using as described in example 77 by using 1-bromo-2-methylsulfanyl-ethane instead of 1-bromo-2-methoxy-ethane

R_t = 2.33min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 513 $(M+1)^+$ (^{79}Br), 515 $(M+1)^+$ (^{81}Br)

Example 95: 4-Bromo-5-isopropoxymethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

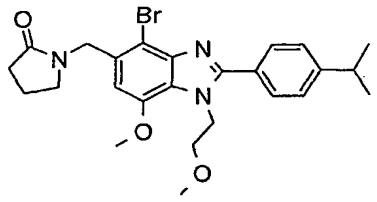


The title compound is prepared using the same methodology as described in example 77 by using 2-propanol (instead of 4-methyl-pyrazole).

R_t = 2.33min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 475 $(M+1)^+$ (^{79}Br), 477 $(M+1)^+$ (^{81}Br)

Example 96: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-pyrrolidin-2-one



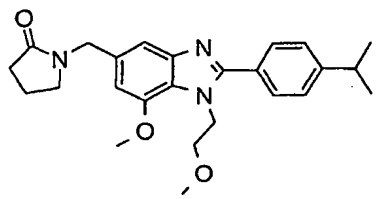
The title compound is prepared from 1-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-pyrrolidin-2-one using the same methodology as described in example 35.

R_t = 2.12 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 500 $(M+1)^+$ (^{79}Br), 502 $(M+1)^+$ (^{81}Br)

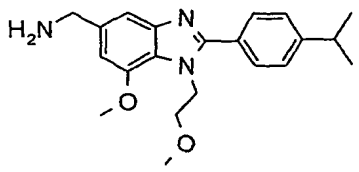
The starting material can be prepared as follows:

a) 1-[2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-pyrrolidin-2-one



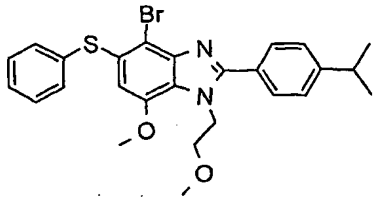
A solution of 50mg (0.143mmol) C-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methylamine, 28mg (0.143mmol) ethyl-4-bromobutyrate and 28µl (0.2mmol) triethylamine in 4ml 3-methyl-1-butanol is stirred at reflux temperature for 8h. Then the reaction mixture is poured on water and extracted (3x) with EtOAc. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (EtOAc:MeOH = 98:2) to afford 20mg of the title compound as a colorless oil.

b) C-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methylamine



To a solution of 100mg (0.286mmol) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbonitrile in 4ml THF, $LiAlH_4$ (54mg, 1.43 mmol) is added. The reaction mixture is stirred at reflux temperature for 2h. After that methanol (0.5ml) and 5ml 15% NaOH-solution is added. This mixture is filtered and the filtrate is extracted (3x) with EtOAc. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford 60mg of the title compound as an oil.

Example 97: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenylsulfanyl-1H-benzoimidazole

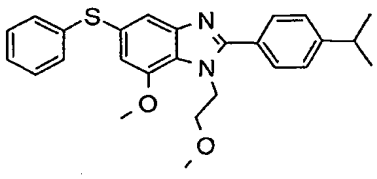


The title compound is prepared from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenylsulfanyl-1H-benzoimidazole using the method described for the preparation of example 35

R_t = 2.49min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

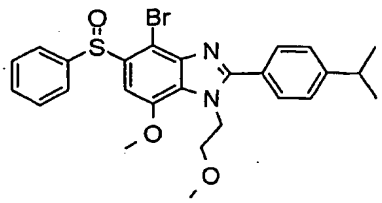
MS: 511 $(M+1)^+$ (^{79}Br), 513 $(M+1)^+$ (^{81}Br)

The starting material 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenylsulfanyl-1H-benzoimidazole can be prepared as follows:



A mixture of 200mg (0.491mmol) 5-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole (example 22), 354mg Cs_2CO_3, 9mg CuI, 56 µl Ph-SH and 2ml N-methylpyrrolidone is stirred at 200°C for 2h. Then the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane : EtOAc = 3:1) to afford 55mg of the title compound as an oil.

Example 98: 5-Benzenesulfinyl-4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole

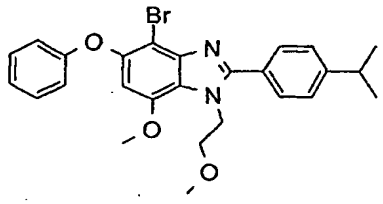


The title compound is prepared from 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenylsulfanyl-1H-benzoimidazole using the method described for the preparation of example 47 (oxidation reaction carried out at 40°C for 4h).

R_t = 2.45min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 527 $(M+1)^+$ (^{79}Br), 529 $(M+1)^+$ (^{81}Br)

Example 98a: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenoxy-1*H*-benzoimidazole

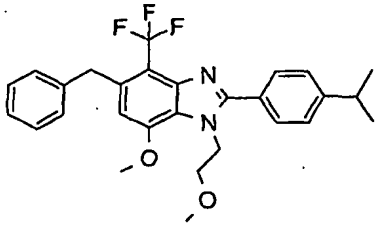


The title compound is prepared using the method described for the preparation of example 97.

R_t = 2.39min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 495 $(M+1)^+$ (^{79}Br), 497 $(M+1)^+$ (^{81}Br)

Example 99: 5-Benzyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole

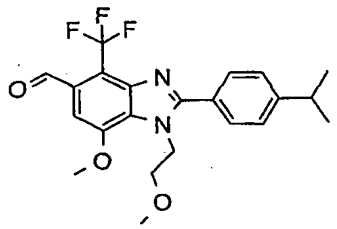


The title compound is prepared from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole-5-carbaldehyde and phenylmagnesiumbromide as described in examples 35 and 51.

R_t = 2.40min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 483 $(M+1)^+$

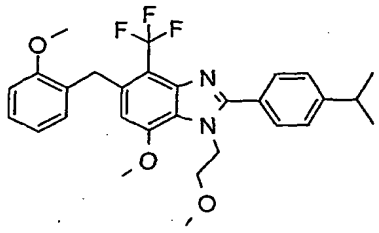
The starting material 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole-5-carbaldehyde can be prepared as follows:



A mixture of 550mg (1.45mmol) 4-Iodo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde (example 26k), 28mg CuI (0.145mmol), 555 µl (4.36mmol) methyl-2,2-difluoro-2-(fluorosulfonyl) acetate and 2ml DMF is stirred at 120°C for 2h. Then the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (100% hexane -> 100% EtOAc) to afford 525mg of the title compound as a colorless crystalline solid.

Using the same method the following compounds are also prepared:

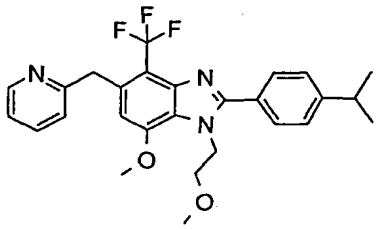
Example 100: 2-(4-Isopropyl-phenyl)-7-methoxy-5-(2-methoxy-benzyl)-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole



R_t = 2.40min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 513 $(M+1)^+$

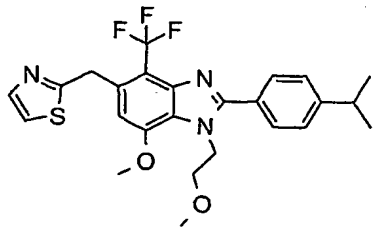
Example 101: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyridin-2-ylmethyl-4-trifluoromethyl-1H-benzoimidazole



R_t = 1.99min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 484 $(M+1)^+$

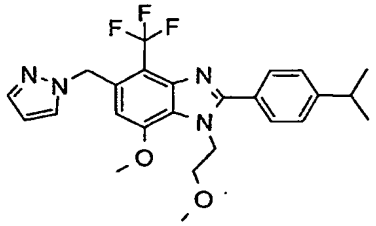
Example 101a: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-thiazol-2-ylmethyl-4-trifluoromethyl-1H-benzoimidazole



R_t = 2.22min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 490 $(M+1)^+$

Example 102: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-pyrazol-1-ylmethyl-4-trifluoromethyl-1H-benzoimidazole



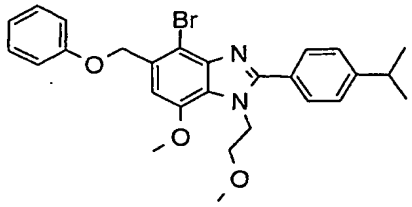
The title compound is prepared from methanesulfonic acid 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl ester and pyrrazole as described in examples 35 and 77.

R_t = 2.25min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 473 $(M+1)^+$

The starting material methanesulfonic acid 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl ester can be prepared from 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole-5-carbaldehyde (see example 99) using the method described for the preparation of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester (example 77).

Example 103: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenoxy methyl-1H-benzoimidazole



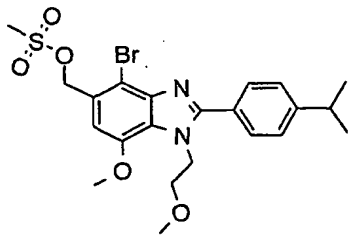
To a cooled solution (ice bath) of phenol (7.2 mg, 0.077mmol) in 1ml DMF, NaH (3.1mg, 0.077mmol, 60% in mineral oil) is added and the reaction is warmed to RT. Methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester (30mg, 0.059mmol) is added and the reaction mixture is heated to 60°C for 1h. After that the reaction mixture is extracted with sat. $NaHCO_3$-solution and diethyl ether. The combined organic layers are washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane:EtOAc = 1:1) to afford 28mg of the title compound as pale yellow crystals.

R_t = 2.42min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 509 $(M+1)^+$ (^{79}Br), 511 $(M+1)^+$ (^{81}Br)

The starting materials can be prepared as described in example 77 (steps a to c) :

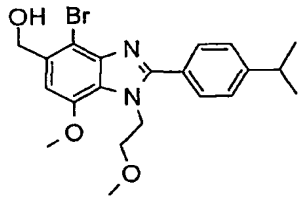
a) Methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester:



A solution of 200mg (0.462mmol) [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol is dissolved in 5 ml CH_2Cl_2. The solution is cooled to 0°C and methanesulfonyl chloride (47ul, 0.600mmol) and Huenig's base (103ul, 0.600mmol) is added. After 1h the reaction is extracted with CH_2Cl_2/10% citric acid. The organic layer is

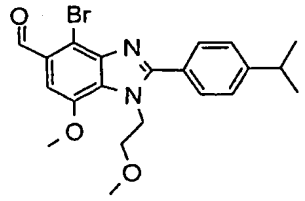
dried over $MgSO_4$, filtered and concentrated in vacuo to give 240mg of material which is used without further purification.

b) [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-yl]-methanol:



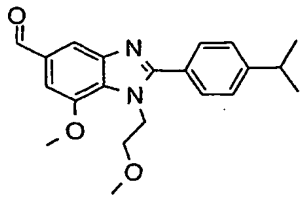
2.08g (4.82mmol) of 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde is dissolved in 60 ml Ethanol and NaBH4 (365mg, 9.64 mmol) is added. After stirring for 30 min ice/water is added and the reaction mixture is extracted with ethyl acetate (3x). The organic layer is washed with water (3x) and brine (2x), dried (Na_2SO_4) and concentrated in vacuo. The residue is crystallized from diethyl ether/hexanes to give 1.85g of colorless crystals.

c) 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde:



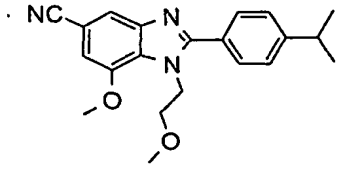
3.0 g (8.51mmol) of 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde is dissolved in 90 ml acetic acid. Bromine (437ul, 8.51mmol) is added dropwise and the reaction is stirred for 5h at RT. Ice/water is added and the reaction mixture is extracted with ethyl acetate (3x). The organic layer is washed with water (3x) and brine (2x), dried (Na_2SO_4) and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexanes/EtOAc) to give 2.08 g of colorless crystals.

d) 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole-5-carbaldehyde:



To a solution of 7.02g (20.1mmol) of 1-(2-Hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole-5-carbonitrile in 280 ml pyridine is added 140 ml acetic acid. After addition of a solution of 14.1g (161mmol) sodium hypophosphite in 140 ml water and heating to 50°C Raney-Nickel is added in 50 mg portions (3x over 12 h) until the reaction is complete. The reaction mixtures is cooled to RT, ice/water is added and the reaction mixture is extracted with ethyl acetate (3x). The organic layer is washed with water, in vacuo and azeotroped with toluene. The residue is suspended in 100ml CH_2Cl_2, filtered and washed with CH_2Cl_2 and ethyl acetate. The mother liquor is evaporated and purified by flash-chromatography on silica gel (hexanes/EtOAc) to give 3.78g of colorless crystals.

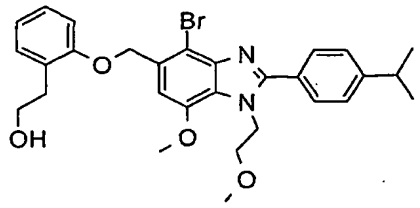
e) 1-(2-Hydroxy-ethyl)-2-(4-isopropyl-phenyl)-7-methoxy-1H-benzoimidazole-5-carbonitrile:



A solution of 1.42g (3.52mmol) of 5-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole and 455 mg (3.87mmol) zinc cyanide in 15 ml DMF is stirred under argon for 10 min at RT. Tetrakis(triphenylphosphine)palladium (214mg, 0.176mmol) is added and the reaction is heated to 180°C for 90 min. After cooling to RT, ice/water is added and the reaction mixture is extracted with ethyl acetate (3x). The organic layer is washed with water, dried (Na_2SO_4) and concentrated in vacuo and the material is used without further purification.

Using the same synthetic method the following examples are prepared:

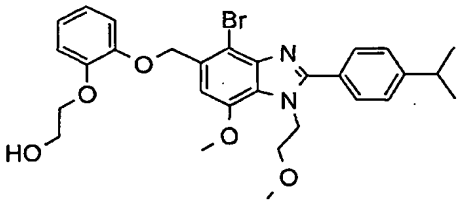
Example 104: 2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-ethanol



R_t = 2.26min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 553 $(M+1)^+$ (^{79}Br), 555 $(M+1)^+$ (^{81}Br)

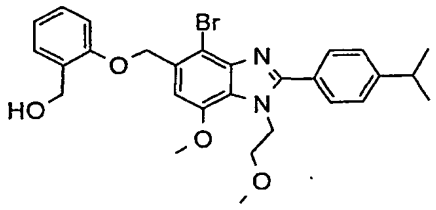
Example 105: 2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol



R_t = 2.21min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 569 $(M+1)^+$ (^{79}Br), 571 $(M+1)^+$ (^{81}Br)

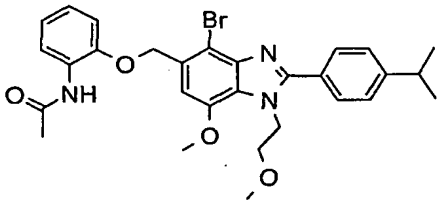
Example 106: {2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-methanol



R_t = 2.22 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 539 $(M+1)^+$ (^{79}Br), 541 $(M+1)^+$ (^{81}Br)

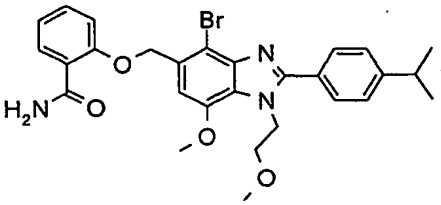
Example 107: N-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-acetamide



R_t = 2.24 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 566 $(M+1)^+$ (^{79}Br), 568 $(M+1)^+$ (^{81}Br)

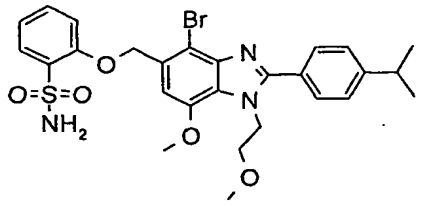
Example 108: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-benzamide



R_t = 2.17 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 552 $(M+1)^+$ (^{79}Br), 554 $(M+1)^+$ (^{81}Br)

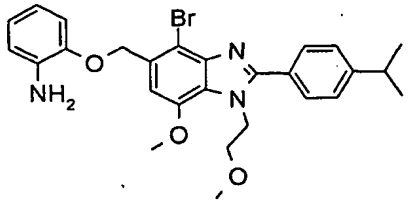
Example 109: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-benzenesulfonamide



R_t = 2.20 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 588 $(M+1)^+$ (^{79}Br), 590 $(M+1)^+$ (^{81}Br)

Example 110: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenylamine

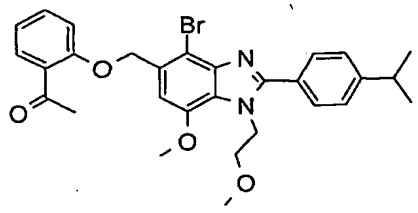


R_t = 1.98min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 524 $(M+1)^+$ (^{79}Br), 526 $(M+1)^+$ (^{81}Br)

Example 111: 1-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-

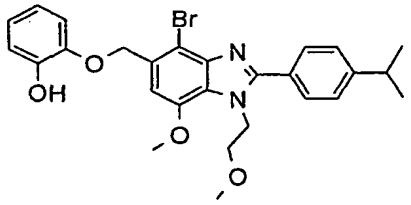
benzoimidazol-5-ylmethoxy]-phenyl}-ethanone



R_t = 2.35 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 551 $(M+1)^+$ (^{79}Br), 553 $(M+1)^+$ (^{81}Br)

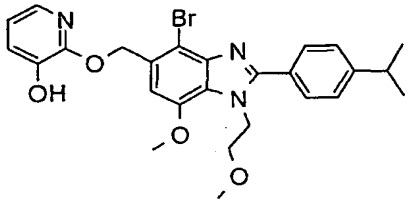
Example 112: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenol



R_t = 2.28 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 525 $(M+1)^+$ (^{79}Br), 527 $(M+1)^+$ (^{81}Br)

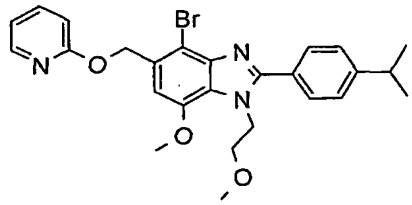
Example 113: 2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-pyridin-3-ol



R_t = 2.01min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 526 $(M+1)^+$ (^{79}Br), 528 $(M+1)^+$ (^{81}Br)

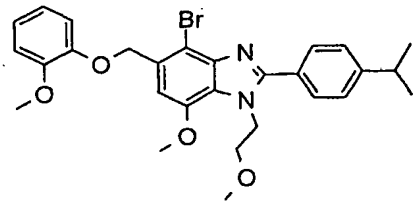
Example 114: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxymethyl)-1H-benzoimidazole



R_t = 2.07 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 510 $(M+1)^+$ (^{79}Br), 512 $(M+1)^+$ (^{81}Br)

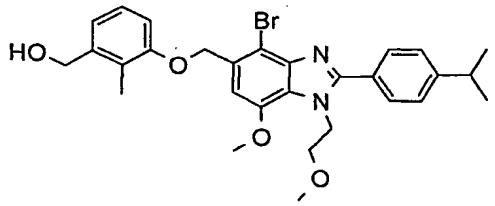
Example 115: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(2-methoxy-phenoxymethyl)-1H-benzoimidazole



R_t = 2.36 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 539 $(M+1)^+$ (^{79}Br), 541 $(M+1)^+$ (^{81}Br)

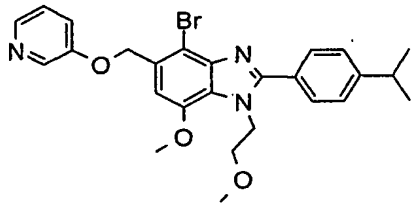
Example 116: {3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-2-methyl-phenyl}-methanol



R_t = 2.24 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 553 $(M+1)^+$ (^{79}Br), 555 $(M+1)^+$ (^{81}Br)

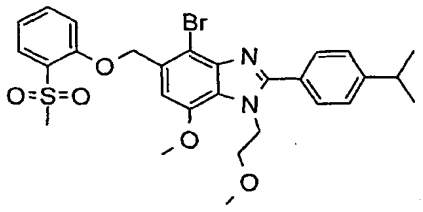
Example 117: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-3-yloxymethyl)-1H-benzoimidazole



R_t = 1.95 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 510 $(M+1)^+$ (^{79}Br), 512 $(M+1)^+$ (^{81}Br)

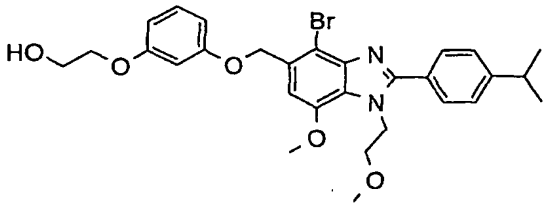
Example 118: 4-Bromo-2-(4-isopropyl-phenyl)-5-(2-methanesulfonyl-phenoxymethyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazole



R_t = 2.28 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 587 $(M+1)^+$ (^{79}Br), 589 $(M+1)^+$ (^{81}Br)

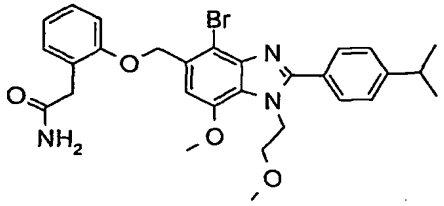
Example 119: 2-{3-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol



R_t = 2.18min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 569 $(M+1)^+$ (^{79}Br), 571 $(M+1)^+$ (^{81}Br)

Example 120: 2-{2-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethoxy]-phenyl}-acetamide

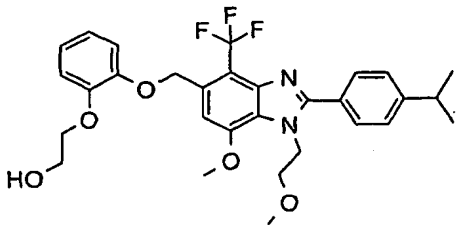


R_t = 2.14 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 566 $(M+1)^+$ (^{79}Br), 568 $(M+1)^+$ (^{81}Br)

Using the same method by using 5-bromomethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole (see example 136) instead of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester the following compounds are prepared:

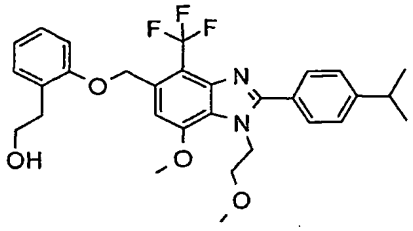
Example 121: 2-{2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-phenoxy}-ethanol



R_t = 2.14 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 559 $(M+1)^+$

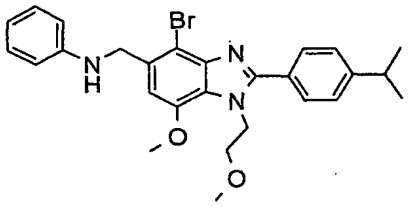
Example 122: 2-{2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-phenyl}-ethanol



R_t = 2.35 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 543 $(M+1)^+$

Example 123: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-phenyl-amine



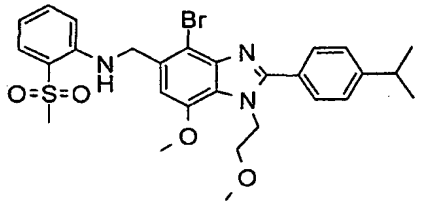
To a solution of 20mg (0.039mmol) of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester in DMF is added aniline (excess) and the reaction is stirred for 1h at 60°C. The reaction mixture is extracted with sat. $NaHCO_3$/water. The organic layer is evaporated and the residue is purified via reversed phase RP18-chromatographie to give 3.3mg of the title compound.

R_t = 2.26min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 508 $(M+1)^+$ (^{79}Br), 510 $(M+1)^+$ (^{81}Br)

Using the same synthetic method the following examples are prepared:

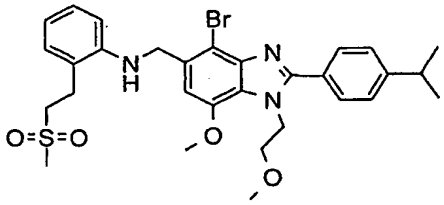
Example 124: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-(2-methanesulfonyl-phenyl)-amine



R_t = 2.29 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 586 $(M+1)^+$ (^{79}Br), 588 $(M+1)^+$ (^{81}Br)

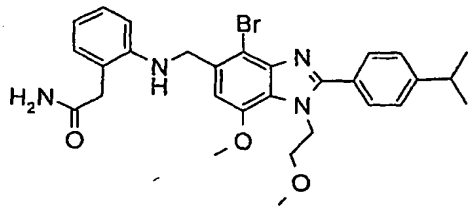
Example 125: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-[2-(2-methanesulfonyl-ethyl)-phenyl]-amine



R_t = 2.23 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 614 $(M+1)^+$ (^{79}Br), 616 $(M+1)^+$ (^{81}Br)

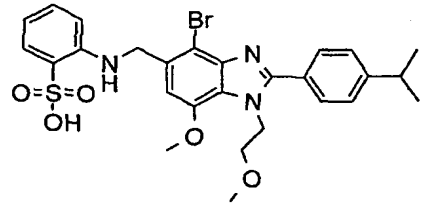
Example 126: 2-(2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-amino}-phenyl)-acetamide



R_t = 2.10 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 565 $(M+1)^+$ (^{79}Br), 567 $(M+1)^+$ (^{81}Br)

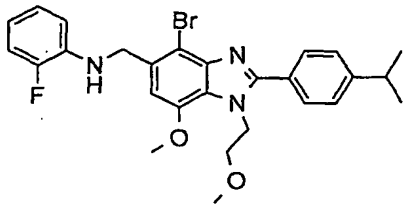
Example 127: 2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-amino}-benzenesulfonic acid



R_t = 2.09 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 586$(M-1)^-$ (^{79}Br), 588 $(M-1)^-$ (^{81}Br)

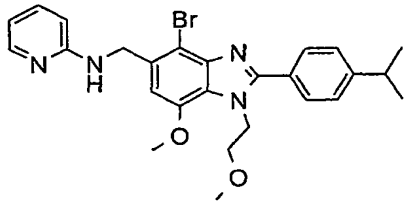
Example 128: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-(2-fluoro-phenyl)-amine



R_t = 2.35 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 526 $(M+1)^+$ (^{79}Br), 528 $(M+1)^+$ (^{81}Br)

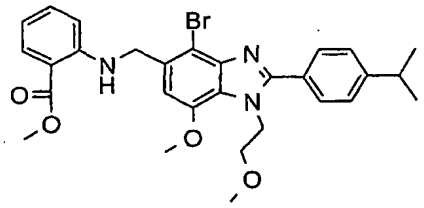
Example 129: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-pyridin-2-yl-amine



R_t = 1.91 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 509 $(M+1)^+$ (^{79}Br), 511 $(M+1)^+$ (^{81}Br)

Example 130: 2-{[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-amino}-benzoic acid methyl ester

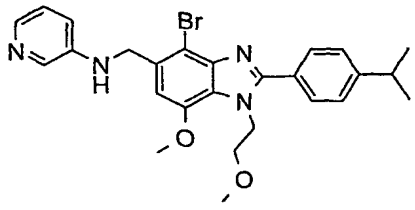


R_t = 2.44 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 566 $(M+1)^+$ (^{79}Br), 568 $(M+1)^+$ (^{81}Br)

Example 131: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo

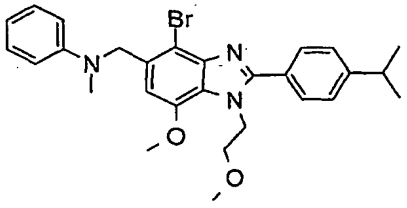
imidazol-5-ylmethyl]-pyridin-3-yl-amine



R_t = 1.89 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 509 $(M+1)^+$ (^{79}Br), 511 $(M+1)^+$ (^{81}Br)

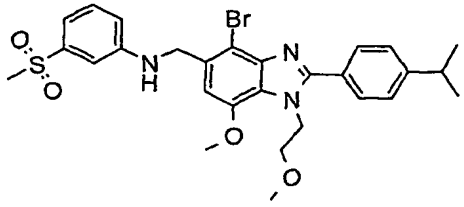
Example 132: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-methyl-phenyl-amine



R_t = 2.34 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 522 $(M+1)^+$ (^{79}Br), 524 $(M+1)^+$ (^{81}Br)

Example 133: [4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzo imidazol-5-ylmethyl]-(3-methanesulfonyl-phenyl)-amine

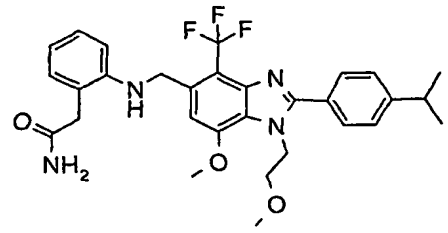


R_t = 2.18 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 586 $(M+1)^+$ (^{79}Br), 588 $(M+1)^+$ (^{81}Br)

Using the same method by using 5-bromomethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole instead of methanesulfonic acid 4-bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl ester the following compound are prepared:

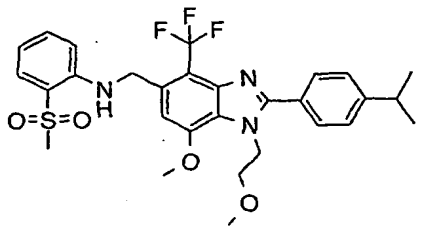
Example 134: 2-(2-{[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-amino}-phenyl)-acetamide



R_t = 2.19 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 555 $(M+1)^+$

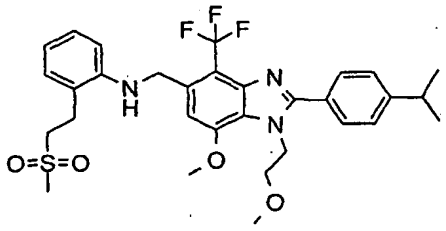
Example 135: [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-(2-methanesulfonyl-phenyl)-amine



R_t = 2.36 min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 576 $(M+1)^+$

Example 136: [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-[2-(2-methanesulfonyl-ethyl)-phenyl]-amine

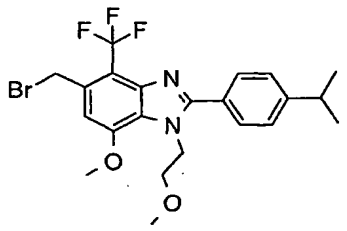


R_t = 2.32min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 604 $(M+1)^+$

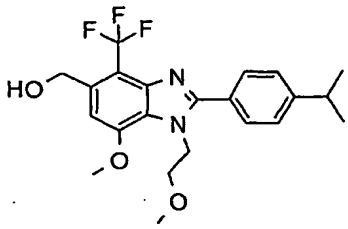
Preparation of the starting material:

a) 5-Bromomethyl-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole



To a solution of 655mg (1.52mmol) [2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-yl]-methanol in 10ml THF, 604mg (2.28mmol) triphenylphosphine and 764mg (2.28mmol) carbon tetrabromide are added at 0°C. The mixture is stirred at 0°C for 10min and 30min at room temperature. Then the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by flash-chromatography on silica gel (hexane : EtOAc = 2:1 -> 1:1) to afford 660mg of the title compound as a colorless crystalline solid.

b) [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-yl]-methanol

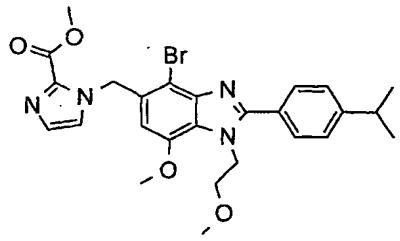


To a solution of 710mg (1.69mmol) 2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazole-5-carbaldehyde (example 54c) in 5ml ethanol, 128mg (3.38mmol) $NaBH_4$ are added at 0°C. The mixture is stirred for 30min at room temperature. Then the reaction mixture is poured on water and extracted (3x) with ethyl acetate. The combined organic layers are washed with water (2x) and brine, dried over $MgSO_4$, filtered

and concentrated in vacuo. The residue is crystallized from hexane/EtOAc to afford 655mg of the title compound as a colorless crystalline solid.

Using the synthetic methods described above the following compounds are also be prepared:

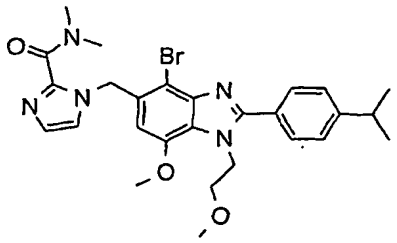
Example 137: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid methyl ester



R_t = 2.05min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 541 $(M+1)^+$ (^{79}Br), 543 $(M+1)^+$ (^{81}Br)

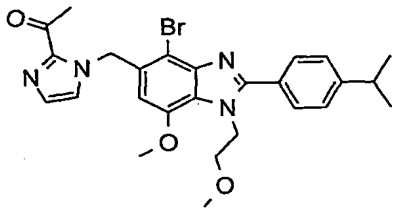
Example 138: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid dimethylamide



R_t = 1.98min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 554 $(M+1)^+$ (^{79}Br), 556 $(M+1)^+$ (^{81}Br)

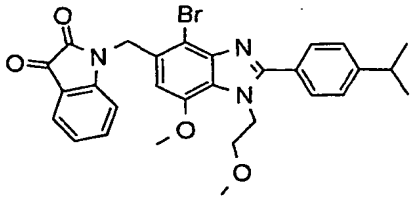
Example 139: 1-{1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazol-2-yl}-ethanone



R_t = 2.12min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 525 $(M+1)^+$ (^{79}Br), 527 $(M+1)^+$ (^{81}Br)

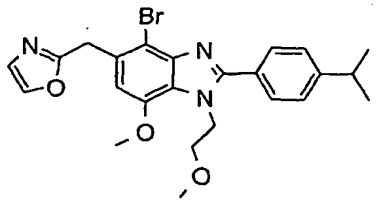
Example 140: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-indole-2,3-dione



R_t = 2.29min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 562 $(M+1)^+$ (^{79}Br), 564 $(M+1)^+$ (^{81}Br)

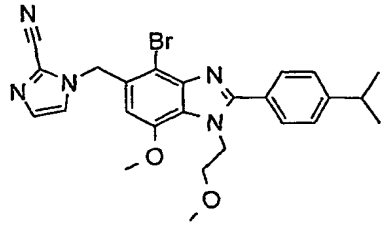
Example 141: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-oxazol-2-ylmethyl-1H-benzoimidazole



R_t = 1.85min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 484 $(M+1)^+$ (^{79}Br), 486 $(M+1)^+$ (^{81}Br)

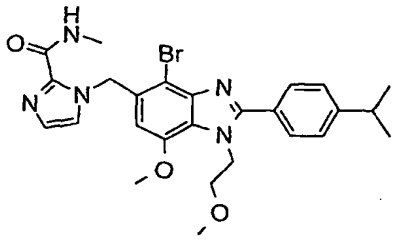
Example 142: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carbonitrile



R_t = 2.24min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 508 $(M+1)^+$ (^{79}Br), 510 $(M+1)^+$ (^{81}Br)

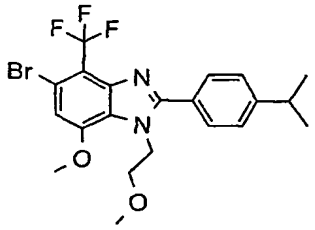
Example 143: 1-[4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-1H-benzoimidazol-5-ylmethyl]-1H-imidazole-2-carboxylic acid methylamide



R_t = 1.79*min* (*Waters Symmetry* C8, 2.1x50*mm*, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 540 $(M+1)^+$ (^{79}Br), 542 $(M+1)^+$ (^{81}Br)

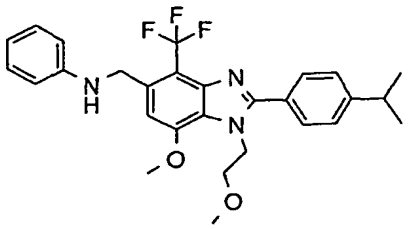
Example 144: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-bromo-4-trifluoromethyl-1H-benzoimidazole



R_t = 2.50min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 471 $(M+1)^+$ (^{79}Br), 473 $(M+1)^+$ (^{81}Br)

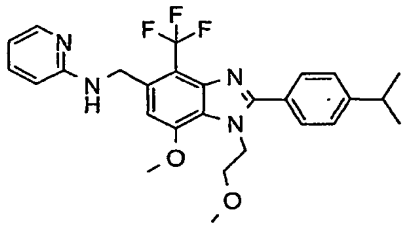
Example 145: [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-phenyl-amine



R_t = 2.35min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 498 $(M+1)^+$

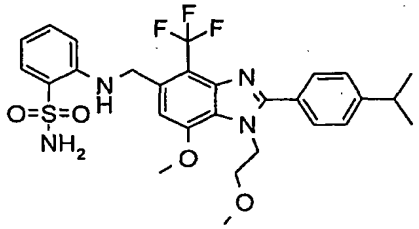
Example 146: [2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-pyridin-2-yl-amine



R_t = 1.97min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 499 $(M+1)^+$

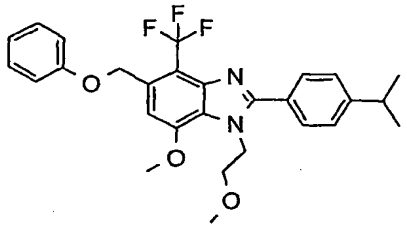
Example 147: 2-{[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethyl]-amino}-benzenesulfonamide



R_t = 2.17min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 577 $(M+1)^+$

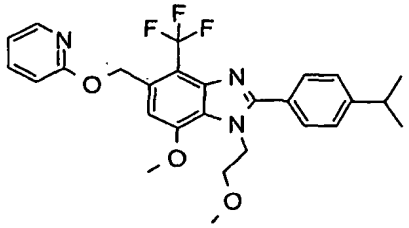
Example 148: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-phenoxymethyl-4-trifluoromethyl-1H-benzoimidazole



R_t = 2.48min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 499 $(M+1)^+$

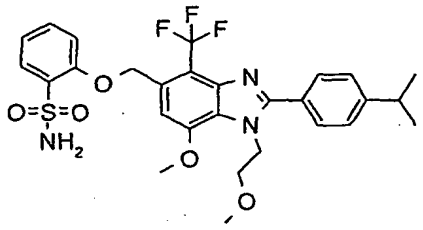
Example 149: 2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxymethyl)-4-trifluoromethyl-1H-benzoimidazole



R_t = 2.14min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 500 $(M+1)^+$

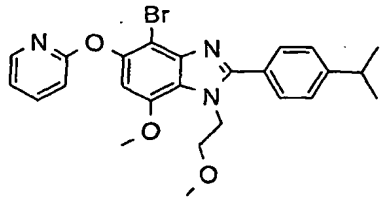
Example 150: 2-[2-(4-Isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-4-trifluoromethyl-1H-benzoimidazol-5-ylmethoxy]-benzenesulfonamide



R_t = 2.29min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 578 $(M+1)^+$

Example 151: 4-Bromo-2-(4-isopropyl-phenyl)-7-methoxy-1-(2-methoxy-ethyl)-5-(pyridin-2-yloxy)-1H-benzoimidazole



R_t = 2.24min (Waters Symmetry C8, 2.1x50mm, detection 210-250nM, 10% to 95% CH_3CN in H_2O in 2min + 0.05% TFA, flow rate 1.0ml/min)

MS: 496 $(M+1)^+$ (^{79}Br), 498 $(M+1)^+$ (^{81}Br)

The Agents of the Invention, as defined above, e.g., of formula (I), particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

Inositol phosphate formation assay:

To determine antagonistic activity at the human parathyroid calcium-sensing receptor (PcaR), compounds are tested in functional assays measuring the inhibition of calcium-induced inositol phosphate formation in CCL39 fibroblasts stably transfected with human PcaR.

Cells are seeded into 24 well plates and grown to confluence. Cultures are then labelled with [^{3}H]inositol (74 Mbq/ml) in serum-free medium for 24h. After labelling, cells are washed once with a modified Hepes-buffered salt solution (mHBS: 130 mM NaCl, 5.4 mM KCl, 0.5 mM $CaCl_2$, 0.9 mM $MgSO_4$, 10 mM glucose, 20 mM HEPES, pH 7.4) and incubated with mHBS at 37 °C in the presence of 20 mM LiCl to block inositol monophosphatase activity. Test compounds are added 3 minutes before stimulating PcaR with 5.5 mM calcium and incubations continued for further 20 min. Thereafter, cells are extracted with 10 mM ice-cold formic acid and inositol phosphates formed are determined using anion exchange chromatography and liquid scintillation counting.

Assay for intracellular free calcium:
An alternative method to determine antagonism at the PcaR consists in measuring the inhibition of intracellular calcium transients stimulated by extracellular calcium.
CCL39 fibroblasts stably transfected with human PcaR are seeded at 40'000 cells /well into 96-well Viewplates and incubated for 24 hours. Medium is then removed and replaced with fresh medium containing 2 µM Fluo-3 AM (Molecular Probes, Leiden, The Netherlands), In routine experiments, cells are incubated at 37°C, 5 % CO_2 for 1 h. Afterwards, plates are washed twice with mHBS and wells are refilled with 100 µl mHBS containing the test compounds. Incubation is continued at room temperature for 15 minutes. To record changes of intracellular free calcium, plates are transferred to fluorescence-imaging plate reader (Molecular Devices, Sunnyvale, CA, USA). A baseline consisting in 5 measurements of 0.4 seconds each (laser excitation 488 nm) is recorded. Cells are then stimulated with calcium (2.5 mM final), and fluorescence changes recorded over a period of 3 minutes.

When measured in the above assays, Agents of the Invention typically have IC_{50}s in the range from about 1000 nM down to about 10 nM or less.

It is now well established that controlled treatment of patients with parathyroid hormone (PTH) and analogues and fragments thereof can have a pronounced anabolic effect on bone formation. Thus compounds which promote PTH release, such as the Agents of the

Invention may be used for preventing or treating conditions of bone which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Agents of the Invention are accordingly indicated for preventing or treating all bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable, e.g. osteoporosis of various genesis (e.g. juvenile, menopausal, post-menopausal, post-traumatic, caused by old age or by cortico-steroid therapy or inactivity), fractures, osteopathy, including acute and chronic states associated with skeletal demineralisation, osteo-malacia, periodontal bone loss or bone loss due to arthritis or osteoarthritis or for treating hypoparathyroidism.

Further diseases and disorders which might be prevented or treated include e.g. seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, congestive heart failure; hypertension; gut motility disorders such as diarrhea, and spastic colon and dermatological disorders, e.g. in tissue healing, for example burns, ulcerations and wounds.

The Agents of the Invention are particularly indicated for preventing or treating osteoporosis of various genesis.

For all the above uses, an indicated daily dosage is in the range from about 0.03 to about 1000 mg, preferably , more preferably 0.03 to 30, yet more preferably 0.1 to 10 mg of a compound of the invention. Agents of the Invention may be administered twice a day or up to twice a week.

The Agents of the Invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds. The present invention also provides a pharmaceutical composition comprising an Agent of the Invention in free base form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable

diluent or carrier. Such compositions may be formulated in conventional manner. The Agents of the Invention may be administered by any conventional route, for example parenterally e.g. in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules or in a transdermal, nasal or a suppository form.

In accordance with the foregoing the present invention further provides:

a) an Agent of the Invention or a pharmaceutically acceptable salt thereof for use as a pharmaceutical;

b) a method for preventing or treating above mentioned disorders and diseases in a subject in need of such treatment, which method comprises administering to said subject an effective amount of an Agent of the Invention or a pharmaceutically acceptable salt thereof;

c) an Agent of the Invention or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition e.g. for use in the method as in b) above.

According to a further embodiment of the invention, the Agents of the Invention may be employed as adjunct or adjuvant to other therapy, e.g. a therapy using a bone resorption inhibitor, for example as in osteoporosis therapy, in particular a therapy employing calcium, a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin, a steroid hormone, e.g. an estrogen, a partial estrogen agonist or estrogen-gestagen combination, a SERM (Selective Estrogen Receptor Modulator) e.g. raloxifene, lasofoxifene, TSE-424, FC1271, Tibolone (Livial ®), vitamin D or an analog thereof or PTH, a PTH fragment or a PTH derivative e.g. PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH_2 or PTS 893.

When the Agents of the Invention are administered in conjunction with, e.g. as an adjuvant to bone resorption inhibition therapy, dosages for the co-administered inhibitor will of course vary depending on the type of inhibitor drug employed, e.g. whether it is a steroid or a calcitonin, on the condition to be treated, whether it is a curative or preventive therapy, on the regimen and so forth.